A PHASE 3, RANDOMIZED, ACTIVE-CONTROLLED, OBSERVER-BLINDED TRIAL TO ASSESS THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF MenABCWY IN HEALTHY PARTICIPANTS ≥10 TO <26 YEARS OF AGE

Investigational Product Number:	PF-06886992
Investigational Product Name:	*Neisseria meningitidis* Group A, B, C, W, and Y Vaccine (MenABCWY)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
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Phase:	3

Short Title

Phase 3 MenABCWY Noninferiority Study in Healthy Participants ≥10 to <26 Years of Age

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Amendment 2	13 June 2022	Protocol Sections 1.1, 3, and 9.4.1: Moved MenB secondary strain immunogenicity objective from Secondary Immunogenicity Objectives to Tertiary/Exploratory Objectives. Protocol Sections 5.2.1.1, 6.5.1, and 6.5.2: Made allowance for coronavirus disease 2019 (COVID-19) vaccinations within 8 days of study vaccination instead of 14 days (per the protocol administrative change letter [PACL] dated 01 July 2021). Protocol Section 8.1.1.2: Removal of the text related to secondary strain testing.
Amendment 1	30 April 2021	Protocol Sections 1.2, 1.3, 4.1, 8, 8.1.1, and 8.10.1.4: Added an optional increase in the volume of the blood draws at Visit 4 for the immunogenicity subset from 25 to 50 mL, to support assay development. The volume of blood drawn will depend on the consent obtained. Throughout the protocol: The term "CT SAE Report Form" has been replaced with "Vaccine SAE Reporting Form," as per the PACL dated 08 May 2020. Protocol Section 10.4.3, Woman of Childbearing Potential (WOCBP): The definition of postmenopausal state has been amended, as per the PACL dated 08 October 2020.

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		Protocol Section 4.1, Overall Design, and protocol summary: Administrative clarification: • Estimated that an 80%/20% ratio of US/EU participants is a target relevant to the immunogenicity subset and the overall study, and not specific to the safety subset. • Immunogenicity and safety groups contribute to the safety data set. Protocol Sections 1.2, 4.1 and 9.2.1,: Clarification that the sponsor may decide to proceed with less than full enrollment if an assessment of power shows that it is sufficient to meet the primary immunogenicity objectives and that this assessment will be done in a completely blinded fashion before any participants are unblinded or the immunogenicity data are accessed. Protocol Section 10.4.1: Text updated to comply with mandatory protocol template text ("Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.").
Original protocol	12 December 2019	Not applicable

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative clarification letter.

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1. PROTOCOL SUMMARY

1.1. Synopsis

In Study B1971057, a first-in-human (FIH) and proof-of-concept (POC) study for *Neisseria meningitidis* group A, B, C, W, and Y vaccine (MenABCWY), 543 participants received MenABCWY on a 0-month and 6-month schedule. Results from B1971057 indicated MenABCWY is well tolerated with an acceptable safety profile, and also provides a high degree of protective immune responses among both meningococcal group A, C, W, and Y (ACWY)-naïve and ACWY-experienced participants without interference among all 5 serogroup components.

The aim of this Phase 3 study is to determine the immunologic noninferiority of MenABCWY, an investigational pentavalent (serogroups A, B, C, W, Y) meningococcal vaccine, to licensed vaccines Trumenba® (serogroup B; bivalent recombinant lipoprotein 2086 vaccine [bivalent rLP2086]) and Menveo (meningococcal groups A, C, Y, and W-135 oligosaccharide diphtheria conjugate vaccine [MenACWY-CRM]) by assessing the safety and immunogenicity of MenABCWY and the comparators in healthy participants ≥10 to <26 years of age who have (ACWY-experienced) and have not (ACWY-naïve) previously received a conjugated ACWY quadrivalent meningococcal vaccine.

Data obtained from prior studies supporting the licensure of the 2 vaccines comprising MenABCWY, meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine (MenACWY-TT; Nimenrix®) and Trumenba, support a favorable benefit-risk assessment for continued study of MenABCWY.

Objectives, Estimands, and Endpoints

Randomization group descriptions are shown in Section 1.2.

Objectives	Estimands	Endpoints
Primary Immunogenicity:	Primary Immunogenicity:	Primary Immunogenicity:
To demonstrate that the immune response for *N meningitidis* group A (MenA), *N meningitidis* group C (MenC), *N meningitidis* group W (MenW), and *N meningitidis* group Y (MenY) induced by 2 doses of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM in both ACWY-naïve and ACWY-experienced participants, separately.	In ACWY-naïve participants receiving at least 1 dose (Group 2) of MenACWY-CRM or 2 doses (Group 1) of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in serum bactericidal assay using human complement (hSBA) titer from baseline for each ACWY test strain, 1 month after Vaccination 2 in Group 1 compared to 1 month after Vaccination 1 in Group 2.	hSBA titer for each of the ACWY test strains.

Objectives	Estimands	Endpoints
	• For participants with a baseline hSBA titer below the limit of detection (LOD; or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16. • For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < lower limit of quantitation (LLOQ) (ie, hSBA titer of 1:8), a 4-fold response is defined as an hSBA titer of ≥4 times LLOQ. • For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer. In ACWY-experienced participants receiving at least 1 dose (Group 4) of MenACWY-CRM or 2 doses (Group 3) of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain, 1 month after Vaccination 2 in Group 3 compared to 1 month after Vaccination 1 in Group 4. • For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16. • For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ (ie, hSBA titer of 1:8), a 4-fold response is defined as an hSBA titer of ≥4 times LLOQ. • For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.	

Objectives	Estimands	Endpoints

To demonstrate that the immune response induced by 2 doses of MenABCWY is noninferior to the immune response induced by 2 doses of Trumenba.	In participants receiving at least 2 doses of investigational product and who are in compliance with the key protocol criteria (evaluable participants):
	• Differences in the percentage of participants achieving an hSBA titer ≥ LLOQ (1:16 for strain A22 and 1:8 for strains A56, B24, and B44) for all 4 primary MenB test strains combined (composite response), in Groups 1 and 3 combined compared to Groups 2 and 4 combined, at 1 month after Vaccination 2.
	• Difference in the percentage of participants achieving at least a 4-fold rise in hSBA titer from baseline for each of the 4 primary MenB test strains, in Groups 1 and 3 combined compared to Groups 2 and 4 combined, at 1 month after Vaccination 2.
	  • For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16.
	  • For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the LLOQ.
	  • For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.
		hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).

Primary Safety:	Primary Safety:	Primary Safety:
To describe the safety profile of MenABCWY, as measured by local reactions, systemic events, adverse events (AEs), serious adverse events (SAEs), newly diagnosed chronic medical conditions (NDCMCs), medically attended AEs (MAEs), and immediate AEs.	In participants receiving at least 1 dose of investigational product, expressed in MenABCWY groups (Groups 1, 3, 5, and 7 combined) and Trumenba groups (Groups 2, 4, 6, and 8 combined): • The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after each vaccination.	• Local reactions (pain, redness, and swelling). • Systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at any injection site, and joint pain). • Use of antipyretic medication.

Objectives	Estimands	Endpoints
	• The percentage of participants reporting at least 1 SAE, at least 1 MAE, and at least 1 NDCMC during the following time periods: o 30 Days after each vaccination. o 30 Days after any vaccination. o During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the second study vaccination [Visit 4]). o During the follow-up phase (from 1 month after the second study vaccination [Visit 4] through 6 months after the second study vaccination [Visit 5]). o Throughout the study (from the first study vaccination [Visit 1] through 6 months after the second study vaccination [Visit 5]). • The percentage of participants reporting at least 1 AE during the following time periods: o 30 Days after each vaccination. o 30 Days after any vaccination. o During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the second study vaccination [Visit 4]). • The percentage of participants reporting at least 1 immediate AE. • The percentage of participants who missed days of school or work because of AEs.	• AEs, SAEs, MAEs, NDCMCs, and immediate AEs. • Days missing from school or work because of AEs.
Secondary Immunogenicity:	Secondary Immunogenicity:	Secondary Immunogenicity:
To demonstrate that the immune response for MenA, MenC, MenW, and MenY induced by 1 dose of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM, in both ACWY-naïve and ACWY-experienced participants, separately.	In ACWY-naïve participants receiving at least 1 dose of investigational product and who are in compliance with the key protocol criteria (evaluable participants): • Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain, 1 month after Vaccination 1 in Group 1 compared to Group 2.	hSBA titer for each of the ACWY test strains.

Objectives	Estimands	Endpoints
	• For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16. • For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ (ie, hSBA titer of 1:8), a 4-fold response is defined as an hSBA titer of ≥4 times LLOQ. • For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer. In ACWY-experienced participants receiving at least 1 dose of investigational product and who are in compliance with the key protocol criteria (evaluable participants): • Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain, 1 month after Vaccination 1 in Group 3 compared to Group 4. • For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16. • For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ (ie, hSBA titer of 1:8), a 4-fold response is defined as an hSBA titer of ≥4 times LLOQ. • For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.	

Overall Design

This is a Phase 3, randomized, active-controlled, observer-blinded multicenter trial in which approximately 2413 participants ≥10 to <26 years of age will be randomly assigned to receive either MenABCWY and saline, or Trumenba and MenACWY-CRM, as shown in Section 1.2. The study will include evaluation of both ACWY-naïve and ACWY-experienced individuals. All participants will be naïve to any meningococcal group B vaccine prior to enrollment.

Participants in Groups 1 through 4 will be considered an immunogenicity subset, and will contribute to both the safety and immunogenicity analyses; these participants will have blood drawn prior to Vaccination 1 and 1 month after Vaccinations 1 and 2. Participants in Groups 5 through 8 will be considered a safety subset and will contribute to the safety analysis only, and will not have blood drawn for immunogenicity evaluations.

Randomization will be stratified by prior vaccination history. Overall, approximately 1225 ACWY-naïve and 1188 ACWY-experienced participants (having received 1 dose of Menactra or Menveo ≥4 years prior to the date of randomization) will be enrolled. Of these total participants, up to 675 ACWY-naïve and 1013 ACWY-experienced participants will contribute to the immunogenicity subset.

Participants enrolled in the immunogenicity subset will contribute to both immunogenicity and safety evaluations. Additionally, participants will be enrolled in a safety subset that will contribute exclusively to the safety evaluation. Numbers enrolled in the safety subset will therefore be based on numbers needed to achieve an overall number of enrolled participants, all of whom will contribute to the safety evaluation. Numbers stated in the protocol to be enrolled by group across immunogenicity and safety subsets (Section 1.2 and Table 1) are estimates only.

Additionally, randomization will be stratified by geographic region. The overall participant distribution by region will be approximately 80% from the US and approximately 20% from other regions. Among the participants in the immunogenicity subset, approximately 80% will be enrolled in US investigative sites, and approximately 20% will be enrolled in other regions. Regional or safety/immunogenicity group enrollment shifts may be necessary based on the availability of participants with specific characteristics (age group or ACWY experience) in a given location based on local immunization practices. However, these minor shifts from the originally targeted numbers will not deviate from original targets to a degree that will impact the overall study design or endpoint assessments of the study.

Enrollment targets will also be adjusted to achieve appropriate representation by age group (participants 10 to <18 years old and participants 18 to <26 years old) within each subset, and ACWY strata within each subset.

Approximately 2413 participants will be enrolled, and each participant will participate in the study for approximately 12 months.

Statistical Methods

The first primary objective is designed to assess if the immune response induced by 2 doses of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM, for ACWY-naïve and for ACWY-experienced participants separately. This will be assessed as the difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain, 1 month after Vaccination 2 in Groups 1 and 3 separately (MenABCWY groups) compared to 1 month after Vaccination 1 in Groups 2 and 4 separately (MenACWY-CRM groups) using a noninferiority criterion of -10%. The first secondary immunogenicity objective is also designed to assess the noninferiority in MenA, MenC, MenW, and MenY responses in the MenABWCY groups compared to the MenACWY-CRM groups, using the same criterion; this comparison will be made 1 month after Vaccination 1 in Groups 1 and 3 separately (MenABCWY groups) compared to Groups 2 and 4 separately (MenACWY-CRM groups).

The second primary objective is designed to assess if the immune response for MenB induced by 2 doses of MenABCWY is noninferior to the immune response induced by 2 doses of Trumenba. This will be assessed using:

1. the differences in the percentage of participants achieving an hSBA titer ≥ LLOQ (1:16 for strain A22 and 1:8 for strains A56, B24, and B44) for all 4 primary MenB test strains combined (composite response), in the MenABCWY groups compared to the Trumenba groups, at 1 month after Vaccination 2, and

2. the difference in the percentage of participants achieving at least a 4-fold rise in hSBA titer from baseline for each of the 4 primary MenB test strains, in the MenABCWY groups compared to the Trumenba groups, 1 month after Vaccination 2, using a noninferiority criterion of -10%. The second primary objective will be met if the noninferiority criterion is met for all these MenB endpoints.

The primary safety objective will be assessed by descriptive summaries of local reactions, systemic events, use of antipyretic medication, AEs, SAEs, NDCMCs, MAEs, and immediate AEs in the MenABCWY and Trumenba groups as described in Section 9.

1.2. Schema

		Vaccination 1	Follow-up Visit 1[a]	Vaccination 2	Follow-up Visit 2[a]	Telephone Contact
	Approximate Month	**0**	**1**	**6**	**7**	**12**
	Visit Number	**1**	**2**	**3**	**4**	**5**
ACWY-naïve participants	Group 1 (n=450)	MenABCWY + saline		MenABCWY		
	Group 2 (n=225)	Trumenba + MenACWY-CRM		Trumenba		
ACWY-experienced participants	Group 3 (n=675)	MenABCWY + saline		MenABCWY		
	Group 4 (n=338)	Trumenba + MenACWY-CRM		Trumenba		
	Blood draw (Groups 1-4 only)	25 mL	25 mL		25 mL or 50 mL	
ACWY-naïve participants	Group 5 (n=500)	MenABCWY + saline		MenABCWY		
	Group 6 (n=50)	Trumenba + MenACWY-CRM		Trumenba		
ACWY-experienced participants	Group 7 (n=125)	MenABCWY + saline		MenABCWY		
	Group 8 (n=50)	Trumenba + MenACWY-CRM		Trumenba		

a. Follow-up Visits 1 and 2 will be telephone contacts for safety-assessment-only participants in Groups 5 through 8, for whom blood samples will not be obtained.

A portion of the projected number of participant enrollment slots may be moved from the safety subset to the immunogenicity subset to achieve appropriate regional distribution for the overall study population and the immunogenicity subset. This determination will be made by the sponsor while still blinded. The sponsor may decide to proceed with less than full enrollment if an assessment of power shows that it is sufficient to meet the primary objectives. This assessment will be done in a completely blinded fashion before any participants are unblinded or the immunogenicity data are accessed.

1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit ID	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Visit Description	**Vaccination 1**	**Follow-up Visit 1[a]**	**Vaccination 2**	**Follow-up Visit 2[a]**	**Telephone Contact**
Approximate Month	**0**	**1**	**6**	**7**	**6 Months After Last Study Vaccination**
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**173 to 194 Days After Visit 1**	**28 to 42 Days After Visit 3**	**168 to 196 Days After Last Vaccination**
Informed consent	X				
Review eligibility criteria	X				
Demography	X				
Confirm continued eligibility[b]		X	X	X	
Medical history and physical examination	X				
Record previous PRP-OMP vaccinations	X				
Record any previous meningococcal vaccinations	X				
Urine pregnancy test for female participants (obtain results prior to vaccination)	X		X		
Oral temperature (prior to vaccination)	X		X		
Randomization	X				
Obtain blood sample for participants in the immunogenicity subset (Groups 1-4 only) prior to vaccination	25 mL	25 mL		25 mL (or 50 mL[c])	
Investigational product administration and observation[d]	X		X		
Record nonstudy vaccinations		X	X	X	

Visit ID	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Visit Description	**Vaccination 1**	**Follow-up Visit 1[a]**	**Vaccination 2**	**Follow-up Visit 2[a]**	**Telephone Contact**
Approximate Month	**0**	**1**	**6**	**7**	**6 Months After Last Study Vaccination**
Visit Window	**Day 1**	**28 to 42 Days After Visit 1**	**173 to 194 Days After Visit 1**	**28 to 42 Days After Visit 3**	**168 to 196 Days After Last Vaccination**
Provide participant with an e-diary, caliper, measuring tape/ruler, and digital thermometer, if necessary, and provide instructions on use	X		X		
Review and collect e-diary		X		X	
Assess reactogenicity and record use of antipyretic medications[e]	Days 1 to 7		Days 1 to 7		
Provide the participant with a contact card	X				
Provide the participant with a memory aid			X		
Complete Study Visit/Telephone Contact AE Checklist[f]		X	X	X	X
Record concomitant medications used to treat AEs	X	X	X	X	X
(S)AE collection appropriate for the visit[g]	X	X	X	X	X

Abbreviations: e-diary = electronic diary; PRP-OMP = polyribosylribitol phosphate oligosaccharide of *Haemophilus influenzae* type b conjugated to outer membrane protein.

a. Follow-up Visits 1 and 2 will be telephone contacts for safety-assessment-only participants in Groups 5 through 8, for whom blood samples will not be obtained.
b. Ensure that the participant continues to be eligible for the study, and continues to comply with contraception requirements, as appropriate.
c. In the subset of participants ≥16 years of age.
d. Observe the participant for at least 30 minutes (or longer as per local practice) after the investigational product administration for any acute reactions.
e. Between visits, review the e-diary data online at frequent intervals. Contact the parent(s)/legal guardian or the participant in order to obtain stop dates for any local reactions, systemic events, or use of antipyretic medication that were ongoing on the last day that the e-diary was completed.
f. Checklist includes questions regarding newly diagnosed chronic medical conditions, medically attended adverse events, and missed days of school or work, as well as about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.
g. Please refer to Section 8.3.1 of the protocol.

2. INTRODUCTION

Bivalent rLP2086 (120 µg) and MenACWY-TT (5 µg of each of the 4 meningococcal polysaccharides A, C, W-135, and Y conjugated to 44 µg of tetanus toxoid) are available commercially as Trumenba® and Nimenrix®, respectively.

Pfizer intends to develop a pentavalent meningococcal vaccine (MenABCWY) by combining bivalent rLP2086 (supplied as a 0.7-mL prefilled syringe [PFS]) and MenACWY-TT. The target indication for the candidate pentavalent vaccine is active immunization to prevent invasive disease caused by *N meningitidis* groups A, B, C, W, and Y in individuals 10 through 25 years of age, regardless of prior exposure to a conjugated ACWY quadrivalent meningococcal vaccine.

Trumenba is composed of 2 recombinant lipidated factor H binding protein (fHBP) variants from MenB, one from fHBP subfamily A and one from subfamily B (A05 and B01, respectively), and is indicated for active immunization to prevent invasive disease caused by MenB. Trumenba is approved for use in individuals 10 through 25 years of age in the United States and individuals 10 years of age and older in Europe and other locations.

Nimenrix is composed of capsular polysaccharides from each of the A, C, W, and Y groups of *N meningitidis* conjugated to tetanus toxoid, and is indicated for active immunization of individuals 6 weeks of age and older against invasive meningococcal diseases caused by *N meningitidis* groups A, C, W-135, and Y and is approved in Europe and other locations.

2.1. Study Rationale

In Study B1971057, an FIH and POC study for MenABCWY, 543 participants received MenABCWY on a 0-month and 6-month schedule. Results from B1971057 indicated MenABCWY is well tolerated with an acceptable safety profile, and also provides a high degree of protective immune responses among both ACWY-naïve and ACWY-experienced participants without interference among all 5 serogroup components.

The aim of this Phase 3 study is to determine the immunologic noninferiority of MenABCWY to licensed vaccines Trumenba and MenACWY-CRM (Menveo) by assessing the safety and immunogenicity of MenABCWY and the comparators in both ACWY-naïve and ACWY-experienced healthy participants ≥10 to <26 years of age.

Data obtained from prior studies supporting the licensure of the 2 vaccines comprising MenABCWY, Nimenrix and Trumenba, support a favorable benefit-risk assessment for continued study of MenABCWY.

2.2. Background

2.2.1. Background of the Disease and Medical Need

N meningitidis is an obligate human pathogen that colonizes the upper respiratory tract, which, in some individuals, can cause serious, life-threatening invasive meningococcal disease (IMD), which clinically presents as septicemia, meningitis, or both.[1] *N meningitidis* serogroups A, B, C, W, and Y are 5 of the 6 meningococcal serogroups that cause the vast majority of meningococcal disease globally,[2] and disease incidence is highest in infants and children younger than 5 years of age, adolescents and young adults (16 to 21 years), and older adults (≥65 years).[3] In the United States, meningococcal disease is primarily caused by groups B, C, W, and Y, which are responsible for approximately 79% of disease across all ages.[4]

Current preventive vaccination strategies generally require separate immunizations at different times for an ACWY conjugate vaccine as well as a separate serogroup B vaccine. In the United States, MenACWY vaccination rates among adolescents 13 to 17 years of age are estimated to be 86.6% for ≥1 dose and 50.8% for ≥2 doses, and MenB vaccination coverage among 17-year-olds approaches only 17.2%.[5] In the United States and Europe, MenB has become the most common cause of IMD over the past several years. In the United States, MenB now exceeds all other serogroups in incidence, accounting for 85% of IMD among individuals 11 to 23 years of age, with C, W, and Y accounting for the remainder despite high vaccination rates in targeted adolescents.[4,6] These data support the idea that all 5 serogroups contribute to disease in adolescents and young adults and that a multivalent vaccine incorporating serogroup B would have significant public health utility.

Temporal variations in IMD incidence occur naturally. In industrialized countries, disease rates range from 0.1 cases per 100,000 individuals during endemic periods to 5 to 15 or more cases per 100,000 individuals during prolonged epidemics.[7,8,9,10] During 2017, the incidence of IMD in the United States in young adolescents (11 to 15 years) was 0.04 while at the same time much higher, 0.2, in 16- to 23-year-olds.[4] Although the overall incidence of endemic IMD is quite low, it can rise significantly during epidemics, particularly on US college campuses, where it has been as high as high as 21.1 to 134 per 100,000 in data reported in 2014.[11,12]

In the United States, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) recommends that children 11 to 12 years of age should receive a MenACWY conjugate vaccination with a booster dose at 16 years of age and that adolescents and young adults 16 to 23 years of age may be vaccinated with a MenB vaccine to provide short-term protection against most strains of serogroup B meningococcal disease. Given that meningococcal serogroups B, C, W, and Y cause disease in the United States through early adolescence and young adulthood, with unacceptable mortality and morbidity outcomes with an increasing contribution of serogroup B to IMD in this age group, a safe and effective pentavalent vaccine, which is currently not available, would fulfill an unmet need for broad protection against IMD that is more durable in the setting of the disease's changing epidemiology.[13]

2.2.2. Prior Clinical Experience

2.2.2.1. Trumenba

Trumenba was approved on 29 October 2014, under 21 Code of Federal Regulations (CFR) 601 Subpart E - Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses, for active immunization of individuals 10 through 25 years of age to prevent invasive disease caused by meningococcal group B.

Trumenba was subsequently approved in the European Union (EU) on 24 May 2017 for active immunization of individuals 10 years of age and older to prevent IMD caused by MenB. Trumenba has received marketing authorization in 45 countries and is currently marketed in 22 countries.

Approval of Trumenba was based on the demonstration of safety and a serological correlate that showed in Phase 2 studies the induction of serum bactericidal activity against 4 serogroup B strains that are representative of prevalent US strains. These were measured using hSBAs. As a requirement of licensure, Phase 3 studies were conducted to confirm the safety and immune responses associated with the 3-dose schedule. As of 28 April 2019, it is estimated that 23,586 participants have participated in the Trumenba clinical development program: 12,027 participants were exposed to Trumenba alone; a total of 5202 participants received Trumenba in combination with: diphtheria, tetanus, and acellular pertussis and *Haemophilus influenzae* type b vaccine (DTaP-Hib); hepatitis B virus and inactivated poliomyelitis virus vaccine (HBV-IPV)/Prevenar® (32); diphtheria, tetanus, and acellular pertussis and inactivated poliomyelitis virus vaccine (DTaP-IPV) (372); human papillomavirus vaccine (HPV4) (992); quadrivalent meningococcal polysaccharide conjugate and diphtheria, tetanus, and acellular pertussis vaccine (MCV4-Tdap) (884); MenACWY-CRM (1057); or saline (1865); 543 participants received bivalent rLP2086 mixed with MenACWY-TT (Nimenrix) as a single injection in Study B1971057; and 5847 participants received control. The estimated cumulative worldwide unit distribution for Trumenba from launch through 28 April 2019 is approximately 3,367,496 doses.

A licensure persistence-of-immunity and booster study, B1971033, showed that persistence of immunity after the 2- and 3-dose primary Trumenba series schedules utilized in Studies B1971010 and B1971012 follows similar patterns over 4 years, declining by Year 1 and remaining stable through Year 4, regardless of the primary series schedule. The immune responses following a booster dose with Trumenba 4 years after the primary Trumenba series resulted in generally higher hSBA titers compared to 1 month after the primary series, irrespective of whether participants received a 2-dose or 3-dose series, demonstrating a robust anamnestic response. Protective hSBA titers (hSBA ≥ LLOQ) also persisted in a high proportion of booster recipients (57.5% to 82.8%, depending on the test strain) for up 2 years after the booster dose.

2.2.2.2. Nimenrix (MenACWY-TT)

Nimenrix was first licensed for use in the EU on 20 April 2012 for the active immunization of individuals from the age of 12 months and above against IMD caused by *N meningitidis* serogroups A, C, W-135, and Y. On 12 December 2016, the indication of Nimenrix was extended in Europe to infants 6 weeks of age and older. Nimenrix has received marketing authorization in 83 countries and is currently marketed in 59 countries.

Nimenrix is not presently licensed in the United States, though there is an open investigational new drug application (IND) (BB-IND 13278). Licensure outside of the United States was based on safety and demonstration of immunologic noninferiority (based mainly on comparing proportions of participants with serum bactericidal assay using rabbit complement [rSBA] titers of at least 1:8) to licensed meningococcal vaccines.

Cumulatively, it is estimated that 21,520 participants have participated in the Nimenrix clinical development program (CDP). Worldwide distribution for Nimenrix from launch through 19 April 2019 is approximately 16,124,606 doses.

The immunogenicity studies conducted in participants from 12 months of age and above demonstrate that 1 dose of MenACWY-TT induces a response that is similar to or higher than the response induced by licensed meningococcal vaccines used as control, and that the vaccine is able to induce immunologic memory against the 4 meningococcal serogroups in individuals vaccinated as toddlers 12 to 14 months of age, historically an age group that is not responsive to meningococcal polysaccharide vaccines. Follow-up studies demonstrate that persistence of the responses elicited by the vaccine is similar to or higher than persistence of those elicited by the licensed meningococcal polysaccharide vaccines Meningitec® and Mencevax® when assessed using the GlaxoSmithKline (GSK) rSBA.

2.2.2.3. Pentavalent Meningococcal Vaccine (MenABCWY)

MenABCWY is an investigational pentavalent meningococcal vaccine consisting of bivalent rLP2086 (supplied as a 0.7-mL PFS) and MenACWY-TT, which are administered as a single injection after reconstituting the MenACWY-TT components with the bivalent rLP2086 suspension. MenABCWY has been administered to 543 individuals participating in Study B1971057.

Results from B1971057 demonstrated the immunogenicity and safety of MenABCWY in adolescents and young adults. This was a randomized, active-controlled, observer-blinded multicenter trial in which approximately 1600 participants ≥10 to <26 years of age were randomly assigned to receive either MenABCWY (n=543) on a 0-month and 6-month schedule, or Trumenba on a 0-month and 6-month schedule and MenACWY-CRM (n=1057) at the same time as the first dose of Trumenba. All participants were naïve to any meningococcal group B vaccine prior to enrollment and approximately half were naïve to prior MenACWY vaccination, while the other half were considered ACWY-experienced, having had no more than 1 previous ACWY component vaccine at least 4 years prior to enrollment. Stage 1, which included the vaccination phase of the primary series, is now complete.

Immunogenicity noninferiority evaluations of hSBA responses to the MenACWY component of MenABCWY showed that MenABCWY, both after 1 and 2 doses, was noninferior to a single dose of MenACWY-CRM by 3 different statistical methods for individuals who were either ACWY-naïve or ACWY-experienced. One and 2 doses of MenABCWY were noninferior to 1 dose of MenACWY-CRM at the 10% margin. Specifically, for ACWY-naïve participants, the percentage-of-responder (≥4-fold rise) differences between a single dose of MenABCWY compared to a single dose of MenACWY-CRM were 1.1% (-2.1, 3.7) for serogroup A, 5.5% (-1.3, 11.9) for serogroup C, 10.7% (4.9, 16.1) for serogroup W, and 14.1% (8.1, 19.7) for serogroup Y. Among ACWY-experienced participants, the percentage differences were -0.8% (-4.5, 2.1) for serogroup A, -2.4% (-6.4, 0.9) for C, -0.8% (-4.5, 2.0) for W, and -0.3% (-4.6, 3.3) for Y. Similarly, noninferiority was also established for ≥4-fold rise in the percentage of responders after 2 doses of MenABCWY compared to a single dose of MenACWY-CRM for ACWY-naïve and ACWY-experienced participants.

Among the ACWY-naïve participants, percentage-of-responder differences were 1.1% (-2.2, 3.8) for serogroup A, 26.5% (21.6, 31.1) for C, 21.5% (17.1, 25.8) for W, and 22.9% (17.7, 27.6) for Y. Among the ACWY-experienced participants, differences were -0.8% (-4.7, 2.1) for serogroup A, -0.9% (-4.9, 2.2) for C, -1.9% (-6.1, 1.2) for W, and -1.6% (-6.5, 2.3) for Y. However, GMTs were markedly higher among ACWY-experienced participants than ACWY-naïve participants after MenABCWY administration, indicating the pentavalent vaccine's booster effect for ACWY components. Therefore, MenABCWY, whether given as a single dose, or as a 2-dose series separated by 6 months, was noninferior to a single dose of MenACWY-CRM, regardless of prior ACWY experience.

For the MenB component of MenABCWY, hSBA responses after the second dose were noninferior to those for Trumenba. Noninferiority was established at the 10% margin for percentage of responders who achieved ≥4-fold rise in hSBA titer over baseline among MenABCWY recipients compared to Trumenba recipients for the 4 primary test strains: A22, A56, B24, and B44.

Reactogenicity data were collected for 7 days following each vaccination by electronic diaries (e-diaries) applying the same methodology used in the Trumenba development program. Local and systemic reactogenicity was similar between MenABCWY and Trumenba/MenACWY-CRM recipients, with injection site pain (93.4% vs 91.1%) being the most common local reaction after any vaccination, followed by swelling (26.0% vs 22.4%) and redness (24.5% vs 21.1%). No significant differences among MenABCWY recipients who were considered either ACWY-naïve or ACWY-experienced were observed.

During the vaccination phase (from the first vaccination through 1 month after the second vaccination), similar proportions of participants receiving MenABCWY reported any AE (39.2%) compared to Trumenba + MenACWY-CRM recipients (40.7%), and the 2 groups were also similar between ACWY-naïve and ACWY-experienced MenABCWY recipients. During the same period, similar proportions of participants reported SAEs (1.1% vs 0.8%, respectively), MAEs (26.2% vs 26.7%, respectively), and NDCMCs (0.4% vs 0.8%, respectively). Based on the immunogenicity and safety results from Study B1971057 outlined above, the benefit-risk profile for MenABCWY generated by Phase 2 Study B1971057 is favorable.

2.3. Benefit/Risk Assessment

Trumenba and Nimenrix are licensed vaccines, and common AEs noted after vaccination are primarily related to reactogenicity, including local reactions (pain, swelling, redness around the injection site) and systemic events (headache, fatigue, myalgias, arthralgias, nausea/vomiting, diarrhea, chills, fever). As noted above, the MenABCWY profile from the Phase 2 portion of Study B1971057 is consistent with these 2 licensed products.

As with any vaccine, an allergic reaction may occur. Symptoms of an allergic reaction can include swelling of the lips, mouth, and throat, which may cause difficulty in swallowing or breathing; skin rash; swelling of the hands, feet, and ankles; dizziness; and fainting. A severe allergic shock (anaphylactic shock) may occur. There may also be additional risks related to the vaccines administered in the study that are unknown at this time.

Risks that may be associated with study procedures include risk from blood sampling, such as feeling faint, dizziness, fainting, pain, swelling, bruising, and infection in the vicinity of the vein from where blood is taken.

Safety assessments described in this protocol and ongoing safety data reviews by the investigator, and the sponsor's global medical monitor, the internal safety data review subcommittee, the internal risk management committee, and the external data monitoring committee (E-DMC) will serve to monitor and mitigate these risks.

In Phase 2 Study B1971057, MenABCWY provided a high degree of immunologic protection against IMD caused by *N meningitidis* serogroups A, B, C, W, and Y using the accepted surrogate marker for protective immunity, hSBA ≥ LLOQ, and was statistically noninferior to Trumenba for the B component and MenACWY-CRM for the ACWY components in both ACWY-naïve participants and ACWY-experienced participants. Both populations will be further evaluated to demonstrate noninferiority in the Phase 3 powered study. The proposed Phase 3 clinical trial for MenABCWY is the next step in the pathway for licensure, which, if successful, could provide a broadly protective, safe, comprehensive, and first-in-class meningococcal vaccine that could contribute significantly to a simplified vaccination program for the prevention of IMD.

Pfizer therefore considers that the available information regarding licensed products Trumenba and Nimenrix, as well safety and immunogenicity results from Study B1971057 with MenABCWY, support a favorable benefit-risk profile for MenABCWY in this study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of MenABCWY may be found in the investigator's brochure (IB), which is the single reference safety document (SRSD) for this study. The SRSD is the US package insert (USPI) for Trumenba and USPI for MenACWY-CRM.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary Immunogenicity:	Primary Immunogenicity:	Primary Immunogenicity:

To demonstrate that the immune response for MenA, MenC, MenW, and MenY induced by 2 doses of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM in both ACWY-naïve and ACWY-experienced participants, separately.	In ACWY-naïve participants receiving at least 1 dose (Group 2) of MenACWY-CRM or 2 doses (Group 1) of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants):
	• Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain, 1 month after Vaccination 2 in Group 1 compared to 1 month after Vaccination 1 in Group 2.
	  • For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16.
	  • For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ (ie, hSBA titer of 1:8), a 4-fold response is defined as an hSBA titer of ≥4 times LLOQ.
	  • For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.
	In ACWY-experienced participants receiving at least 1 dose (Group 4) of MenACWY-CRM or 2 doses (Group 3) of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants):
	• Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain, 1 month after Vaccination 2 in Group 3 compared to 1 month after Vaccination 1 in Group 4.
	  • For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16.
	  • For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ (ie, hSBA titer of 1:8), a 4-fold response is defined as an hSBA titer of ≥4 times LLOQ.
		hSBA titer for each of the ACWY test strains.

Objectives	Estimands	Endpoints
	• For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.	
To demonstrate that the immune response for MenB induced by 2 doses of MenABCWY is noninferior to the immune response induced by 2 doses of Trumenba.	In participants receiving at least 2 doses of investigational product and who are in compliance with the key protocol criteria (evaluable participants): • Differences in the percentage of participants achieving an hSBA titer ≥ LLOQ (1:16 for strain A22 and 1:8 for strains A56, B24, and B44) for all 4 primary MenB test strains combined (composite response), in Groups 1 and 3 combined compared to Groups 2 and 4 combined, at 1 month after Vaccination 2. • Difference in the percentage of participants achieving at least a 4-fold rise in hSBA titer from baseline for each of the 4 primary MenB test strains, in Groups 1 and 3 combined compared to Groups 2 and 4 combined, at 1 month after Vaccination 2. • For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16. • For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the LLOQ. • For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.	hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).

Objectives	Estimands	Endpoints
Primary Safety:	Primary Safety:	Primary Safety:

To describe the safety profile of MenABCWY, as measured by local reactions, systemic events, AEs, SAEs, NDCMCs, MAEs, and immediate AEs.	In participants receiving at least 1 dose of investigational product, expressed in MenABCWY groups (Groups 1, 3, 5, and 7 combined) and Trumenba groups (Groups 2, 4, 6, and 8 combined):
	• The percentage of participants reporting local reactions, systemic events, and use of antipyretic medication within 7 days after each vaccination.
	• The percentage of participants reporting at least 1 SAE, at least 1 MAE, and at least 1 NDCMC during the following time periods:
	  • 30 Days after each vaccination.
	  • 30 Days after any vaccination.
	  • During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the second study vaccination [Visit 4]).
	  • During the follow-up phase (from 1 month after the second study vaccination [Visit 4] through 6 months after the second study vaccination [Visit 5]).
	  • Throughout the study (from the first study vaccination [Visit 1] through 6 months after the second study vaccination [Visit 5]).
	• The percentage of participants reporting at least 1 AE during the following time periods:
	  • 30 Days after each vaccination.
	  • 30 Days after any vaccination.
	  • During the vaccination phase (from the first study vaccination [Visit 1] through 1 month after the second study vaccination [Visit 4]).
	• The percentage of participants reporting at least 1 immediate AE.
		• Local reactions (pain, redness, and swelling).
		• Systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at any injection site, and joint pain).
		• Use of antipyretic medication.
		• AEs, SAEs, MAEs, NDCMCs, and immediate AEs.
		• Days missing from school or work because of AEs.

Objectives	Estimands	Endpoints
	• The percentage of participants who missed days of school or work because of AEs.	
Secondary Immunogenicity:	Secondary Immunogenicity:	Secondary Immunogenicity:

To demonstrate that the immune response for MenA, MenC, MenW, and MenY induced by 1 dose of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM, in both ACWY-naïve and ACWY-experienced participants, separately.	In ACWY-naïve participants receiving at least 1 dose of investigational product and who are in compliance with the key protocol criteria (evaluable participants):
	• Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain, 1 month after Vaccination 1 in Group 1 compared to Group 2.
	  • For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16.
	  • For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ (ie, hSBA titer of 1:8), a 4-fold response is defined as an hSBA titer of ≥4 times LLOQ.
	  • For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.
	In ACWY-experienced participants receiving at least 1 dose of investigational product and who are in compliance with the key protocol criteria (evaluable participants):
	• Difference in the percentage of seroresponders, defined as participants achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain, 1 month after Vaccination 1 in Group 3 compared to Group 4.
	  • For participants with a baseline hSBA titer below the LOD (or an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16.
		hSBA titer for each of the ACWY test strains.

Objectives	Estimands	Endpoints
	• For participants with a baseline hSBA titer of ≥ LOD (ie, hSBA titer of ≥1:4) and < LLOQ (ie, hSBA titer of 1:8), a 4-fold response is defined as an hSBA titer of ≥4 times LLOQ. • For participants with a baseline hSBA titer of ≥ LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.	
Tertiary/Exploratory:	Tertiary/Exploratory:	Tertiary/Exploratory:
To describe the immune response for MenA, MenC, MenW, and MenY induced by 2 doses of MenABCWY compared to the immune response induced by 1 dose of MenACWY-CRM, in both ACWY-naïve and ACWY-experienced participants, separately.	In ACWY-naïve and ACWY-experienced participants separately who have received at least 1 dose (Groups 2 and 4) of MenACWY-CRM or 2 doses (Groups 1 and 3) of MenABCWY and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥1:8 for each ACWY test strain, at baseline, 1 month after Vaccination 1 in Groups 2 and 4, and 1 month after Vaccination 2 in Groups 1 and 3. • The percentage of participants achieving hSBA titers of ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each ACWY test strain, at baseline, 1 month after Vaccination 1 in Groups 2 and 4, and 1 month after Vaccination 2 in Groups 1 and 3. • hSBA GMTs for each of the ACWY test strains, at baseline, 1 month after Vaccination 1 in Groups 2 and 4, and 1 month after Vaccination 2 in Groups 1 and 3.	hSBA titer for each of the ACWY test strains.
To describe the immune response for MenA, MenC, MenW, and MenY induced by 1 dose of MenABCWY compared to the immune response induced by 1 dose of MenACWY-CRM, in both ACWY-naïve and ACWY-experienced participants, separately.	In ACWY-naïve and ACWY-experienced participants separately who have received at least 1 dose of investigational product and who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥1:8 for each ACWY test strain, at baseline and 1 month after Vaccination 1 in Groups 1 through 4. • The percentage of participants achieving hSBA titers of ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each ACWY test strain, at baseline and 1 month after Vaccination 1 in Groups 1 through 4. • hSBA GMTs for each of the ACWY test strains, at baseline and 1 month after Vaccination 1 in Groups 1 through 4.	hSBA titer for each of the ACWY test strains.

Objectives	Estimands	Endpoints
To describe the immune response for MenB, as measured by hSBA performed with primary MenB test strains, induced by 2 doses of MenABCWY compared to the immune response induced by 2 doses of Trumenba.	In participants receiving at least 2 doses of investigational product who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ (1:16 for A22 and 1:8 for A56, B24, and B44) for each primary MenB test strain in Groups 1 and 3 combined, and Groups 2 and 4 combined, at baseline and 1 month after Vaccination 2. • The percentage of participants with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB test strains in Groups 1 and 3 combined, and Groups 2 and 4 combined, at baseline and 1 month after Vaccination 2. • hSBA GMTs for each of the 4 primary MenB test strains in Groups 1 and 3 combined, and Groups 2 and 4 combined, at baseline and 1 month after Vaccination 2.	hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44).
To describe the immune response for MenB, as measured by hSBA performed with secondary MenB test strains, induced by 2 doses of MenABCWY.	In participants receiving at least 2 doses of investigational product who are in compliance with the key protocol criteria (evaluable participants): • The percentage of participants achieving an hSBA titer ≥ LLOQ for each secondary MenB test strain in Groups 1 and 3 combined, at baseline and 1 month after Vaccination 2. • The percentage of participants with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each secondary MenB test strain in Groups 1 and 3 combined, at baseline and 1 month after Vaccination 2. • hSBA GMTs for the secondary MenB test strains in Groups 1 and 3 combined, at baseline and 1 month after Vaccination 2.	hSBA titer for each secondary MenB test strain.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, randomized, active-controlled, observer-blinded multicenter trial in which approximately 2413 participants ≥10 to <26 years of age will be randomly assigned to receive either MenABCWY and saline, or Trumenba and MenACWY-CRM, as shown in Table 1. The study will include evaluation of both ACWY-naïve and ACWY-experienced individuals. All participants will be naïve to any meningococcal group B vaccine prior to enrollment.

Participants in Groups 1 through 4 will be considered an immunogenicity subset, and will contribute to both the safety and immunogenicity analyses; these participants will have blood drawn prior to Vaccination 1 and 1 month after Vaccinations 1 and 2. Participants in Groups 5 through 8 will be considered a safety subset and will contribute to the safety analysis only, and will not have blood drawn for immunogenicity evaluations.

Randomization will be stratified by prior vaccination history. Overall, approximately 1225 ACWY-naïve and 1188 ACWY-experienced participants (having received 1 dose of Menactra or Menveo ≥4 years prior to the date of randomization) will be enrolled. Of these total participants, up to 675 ACWY-naïve and 1013 ACWY-experienced participants will contribute to the immunogenicity subset.

Participants enrolled in the immunogenicity subset will contribute to both immunogenicity and safety evaluations. Additionally, participants will be enrolled in a safety subset that will contribute exclusively to the safety evaluation. Numbers enrolled in the safety subset will therefore be based on numbers needed to achieve an overall number of enrolled participants, all of whom will contribute to the safety evaluation. Numbers stated in the protocol to be enrolled by group across immunogenicity and safety subsets (Section 1.2 and Table 1) are estimates only.

Additionally, randomization will be stratified by geographic region. The overall participant distribution by region will be approximately 80% from the US and approximately 20% from other regions. Among the participants in the immunogenicity subset, approximately 80% will be enrolled in US investigative sites, and approximately 20% will be enrolled in other regions. Regional or safety/immunogenicity group enrollment shifts may be necessary based on the availability of participants with specific characteristics (age group or ACWY experience) in a given location based on local immunization practices. However, these minor shifts from the originally targeted numbers will not deviate from original targets to a degree that will impact the overall study design or endpoint assessments of the study.

Enrollment targets will also be adjusted to achieve appropriate representation by age group (participants 10 to <18 years old and participants 18 to <26 years old) within each subset, and ACWY strata within each subset.

Table 1. Study Design

		Vaccination 1	Follow-up Visit 1[a]	Vaccination 2	Follow-up Visit 2[a]	Telephone Contact
	Approximate Month	**0**	**1**	**6**	**7**	**12**
	Visit Number	**1**	**2**	**3**	**4**	**5**
ACWY-naïve participants	Group 1 (n=450)	MenABCWY + saline		MenABCWY		
	Group 2 (n=225)	Trumenba + MenACWY-CRM		Trumenba		
ACWY-experienced participants	Group 3 (n=675)	MenABCWY + saline		MenABCWY		
	Group 4 (n=338)	Trumenba + MenACWY-CRM		Trumenba		
	Blood draw (Groups 1-4 only)	25 mL	25 mL		25 mL or 50 mL	
ACWY-naïve participants	Group 5 (n=500)	MenABCWY + saline		MenABCWY		
	Group 6 (n=50)	Trumenba + MenACWY-CRM		Trumenba		
ACWY-experienced participants	Group 7 (n=125)	MenABCWY + saline		MenABCWY		
	Group 8 (n=50)	Trumenba + MenACWY-CRM		Trumenba		

a. Follow-up Visits 1 and 2 will be a telephone contacts for safety-assessment-only participants in Groups 5 through 8, for whom blood samples will not be obtained.

A portion of the projected number of participant enrollment slots may be moved from the safety subset to the immunogenicity subset to achieve appropriate regional distribution for the overall study population and the immunogenicity subset. This determination will be made by the sponsor while still blinded. The sponsor may decide to proceed with less than full enrollment if an assessment of power shows that it is sufficient to meet the primary objectives. This assessment will be done in a completely blinded fashion before any participants are unblinded or the immunogenicity data are accessed.

4.1.1. Approximate Duration of Participation for Each Participant

Each participant will participate in the study for approximately 12 months.

4.1.2. Approximate Number of Participants

Approximately 2413 participants will be enrolled.

4.2. Scientific Rationale for Study Design

In Study B1971057, an FIH and POC study for MenABCWY, 543 participants received MenABCWY on a 0-month and 6-month schedule. Results from B1971057 indicated MenABCWY is well tolerated with an acceptable safety profile, and also provides a high degree of protective immune responses among both ACWY-naïve and ACWY-experienced participants without interference among all 5 serogroup components.

The aim of this Phase 3 study is to determine the immunologic noninferiority of MenABCWY, an investigational pentavalent (serogroups A, B, C, W, and Y) meningococcal vaccine, to licensed vaccines Trumenba and Menveo (MenACWY-CRM) by assessing the safety and immunogenicity of MenABCWY and the comparators in healthy participants ≥10 to <26 years of age who are both ACWY-naïve and ACWY-experienced.

Data obtained from prior studies evaluating MenABCWY, MenACWY-TT (Nimenrix), and Trumenba support a favorable benefit-risk assessment for continued study of MenABCWY.

4.3. Justification for Dose

Bivalent rLP2086 (120 µg, meningococcal group B vaccine) and MenACWY-TT (5 µg of each of the 4 meningococcal polysaccharides A, C, W-135, and Y conjugated to 44 µg of tetanus toxoid) are available commercially as Trumenba and Nimenrix, respectively. Trumenba is indicated for active immunization to prevent invasive disease caused by MenB, and is approved for use in Europe in individuals 10 years of age and older and in the United States in individuals 10 through 25 years of age. Nimenrix is indicated for active immunization to prevent invasive disease caused by MenA, MenC, MenW, and Men Y, and is approved for use in Europe and a number of ex-US countries, in individuals 6 weeks of age and older. Trumenba is supplied as a 0.5-mL dose PFS, while Nimerix is supplied as a single-dose vial containing lyophilized powder to be reconstituted for injection.

MenABCWY consists of bivalent rLP2086, supplied as a 0.7-mL PFS, which is used to reconstitute MenACWY-TT, and 0.5 mL of the resultant MenABCWY is administered via intramuscular injection.

The safety, tolerability, and immunogenicity of Trumenba and Nimenrix are well established in adolescents and young adults when used separately. Results from Study B1971057, which evaluated MenABCWY on a 0-month and 6-month schedule in adolescents and young adults, showed no clinically significant difference in the tolerability or safety of MenABCWY when compared to Trumenba. Furthermore, no interference was demonstrated for either MenB or ACWY responses when compared to licensed vaccines Trumenba and Menveo in the United States and the EU. Therefore, Pfizer is proceeding with adolescent and adult Phase 3 development of MenABCWY with the dose used in Study B1971057.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including Visit 5 (final telephone contact).

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male and female participants ≥10 and <26 years of age at the time of randomization.

   Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. **ACWY-naïve participants**: Participants who have never received a prior dose of a meningococcal vaccine containing ACWY serogroups. Written confirmation of vaccination history must be obtained prior to randomization.

   ACWY-experienced participants: Participants who have received not more than 1 prior dose, no sooner than 4 years prior to the date of randomization of Menactra or Menveo. Written confirmation of vaccination history must be obtained prior to randomization.

4. Available for the entire study period and can be reached by telephone.

5. Healthy participant as determined by medical history, physical examination, and judgment of the investigator.

6. Male and female participants of childbearing potential must agree to use a highly effective method of contraception for at least 28 days after the last study vaccination. A participant is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active (Appendix 4).

7. Negative urine pregnancy test for all female participants; pregnancy test is not applicable to male participants.

Weight:

Not applicable.

Informed Consent:

8. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. A previous anaphylactic reaction to any vaccine or vaccine-related component.

2. Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate intramuscular injection.

3. A known or suspected defect of the immune system that would prevent an immune response to the vaccine, such as participants with congenital or acquired defects in B-cell function, those receiving chronic systemic (oral, intravenous, or intramuscular) corticosteroid therapy, or those receiving immunosuppressive therapy. Participants in the United States with terminal complement deficiency are excluded from participation in this study. Please refer to the study reference manual (SRM) for additional details.

4. History of microbiologically proven disease caused by *N meningitidis* or *Neisseria gonorrhoeae*.

5. Significant neurological disorder or history of seizure (excluding simple febrile seizure).

6. Any neuroinflammatory or autoimmune condition, including, but not limited to, transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.

7. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation, recent (within the past year) hospitalization for psychiatric illness, or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

8. Previous vaccination with any meningococcal group B vaccine, any purely polysaccharide (nonconjugate) meningococcal vaccine, or monovalent/bivalent meningococcal vaccine. Written vaccination history must be obtained prior to randomization.

9. Participants receiving any allergen immunotherapy with a nonlicensed product or receiving allergen immunotherapy with a licensed product and are not on stable maintenance doses.

10. Receipt of any blood products, including immunoglobulin, within 6 months before the first study vaccination.

11. Current use of systemic antibiotics with no foreseeable date of discontinuation prior to anticipated date of enrollment (first vaccination).

Prior/Concurrent Clinical Study Experience:

12. Participation in other studies involving investigational drug(s) or investigational vaccine(s) within 28 days prior to study entry and/or during study participation.

Diagnostic Assessments:

Not applicable.

Other Exclusions:

13. Investigator site staff members directly involved in the conduct of the study and their family members (including grandchildren), site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.

14. Pregnant female participants; breastfeeding female participants; fertile male participants and female participants of childbearing potential who are unwilling or unable to use a highly effective method of contraception.

5.2.1. Temporary Delay Criteria

5.2.1.1. Criteria for Temporarily Delaying Vaccine Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the conditions have resolved and the participant is eligible for vaccination:

1. Current febrile illness (temperature ≥38.0°C [100.4°F]) or other acute illness within 48 hours before investigational product administration.

2. Participant has received any nonlive vaccine (or intramuscular/sublingual allergen immunotherapy) within 14 days, or any live vaccine within 28 days, before investigational product administration (see exception below for any COVID-19 vaccination).

   Guidance provided by the US Centers for Disease Control and Prevention (CDC) states that COVID-19 vaccines and other vaccines may now be administered without regard to timing. Because of the COVID-19 pandemic and the ongoing COVID-19 vaccinations at the time of study recruitment, participants will be allowed to receive any authorized (nonexperimental) COVID-19 vaccination within 8 days of investigational product administration (ie, not permitted 7 days before or after any study vaccination).

3. Participant is less than 5 days into a course of systemic antibiotic therapy.

4. Participant has received systemic (oral, intravenous, or intramuscular) corticosteroid therapy within the previous 28 days.

If a participant meets any delay criteria for vaccination, all study procedures, including blood sample collection relating to that visit, should be delayed until the day of vaccination. Blood samples must always be collected prior to vaccination.

5.2.1.2. Criteria for Temporarily Delaying Immunogenicity Blood Draw

The following condition is temporary or self-limiting and blood may be drawn once the condition has resolved and the participant is eligible for blood collection:

1. Participant has received systemic antibiotic therapy within the last 5 days (must have a full 5-day interval between the date of the last dose and the date of blood collection).

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to investigational product/entered in the study.

Screen failure data are collected and remain as source and are not reported to the clinical database.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

Trumenba is a 0.5-mL dose supplied as a PFS and formulated to contain 60 µg each of a purified subfamily A and a purified subfamily B rLP2086 protein, 0.15 M sodium chloride, CCI polysorbate 80, and 0.25 mg of Al^{3+} as aluminum phosphate ($AlPO_4$) in 10 mM histidine-buffered saline at pH 6.0.

MenACWY-TT is supplied as a single-dose vial containing lyophilized powder to be reconstituted for injection. The vaccine is formulated on the basis of purified capsular polysaccharide content and the amount of protein carrier is dependent on the polysaccharide-to-protein ratio. The vaccine is nonadjuvanted and preservative-free.

MenACWY-TT will be reconstituted with bivalent rLP2086 supplied as a 0.7-mL PFS, as detailed in the investigational product manual (IP manual), and 0.5 mL of the resultant MenABCWY will be administered via intramuscular injection. The final MenABCWY vaccine composition includes rLP2086 subfamily A and B proteins formulated at 120 µg/mL/subfamily, purified capsular polysaccharides of *N meningitidis* serogroups A, C, W, and Y at concentration of 10 µg/mL/polysaccharide type conjugated to tetanus toxoid at ratios of ~1:3, ~1:3, ~1:1.5, and ~1:1.3, respectively, in 10 mM histidine and 1.2 mM Tris buffer containing 150 mM sodium chloride, 0.5 mg/mL aluminum as $AlPO_4$, 0.035 mg/mL polysorbate 80, and 56 mg/mL sucrose.

MenACWY-CRM (Menveo) is supplied in 2 vials that must be combined prior to administration: the MenA lyophilized conjugate vaccine component is reconstituted with the meningococcal group C, Y, and W-135 (MenCYW-135) liquid conjugate vaccine component immediately before administration as a 0.5-mL intramuscular injection.

The placebo is sterile normal saline solution for injection and will be administered as a 0.5-mL intramuscular injection.

Intervention Name	Trumenba	MenABCWY	MenACWY-CRM	Placebo (Normal Saline)
Dose Formulation	Prefilled syringe 0.5 mL	MenACWY-TT will be reconstituted with bivalent rLP2086, supplied as a 0.7-mL PFS	2 vials	Sterile normal saline solution for injection
Dosage Level(s)	0.5-mL dose at Visits 1 and 3	0.5_mL dose at Visits 1 and 3	0.5-mL dose at Visit 1	0.5-mL dose at Visit 1
Route of Administration	Intramuscular	Intramuscular	Intramuscular	Intramuscular
Investigational Medicinal Product (IMP) and Noninvestigational Medicinal Product (NIMP)	IMP	IMP	IMP	IMP
Sourcing	Pfizer	Pfizer	Commercial	Pfizer
Packaging and Labeling	Study intervention will be provided in a single-dose PFS. Each syringe will be packaged in a carton with a blinded label and a tamper-evident seal, and will be labeled as required per country requirement.	Each MenABCWY kit will consist of a vial of MenACWY-TT, bivalent rLP2086 0.7-mL PFS, and vial adaptor. Kits will be packaged in a carton with a blinded label and a tamper-evident seal, and will be labeled as required per country requirement.	Study intervention will be provided in vials. The vials will be packaged in a carton with a blinded label and a tamper-evident seal, and will be labeled as required per country requirement.	Study intervention will be provided in a single-dose PFS. Each syringe will be packaged in a carton with a blinded label and a tamper-evident seal, and will be labeled as required per country requirement.

6.1.1. Administration

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of investigational products should be performed by an appropriately qualified, Good Clinical Practice (GCP)-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Investigational product administration details will be recorded on the case report form (CRF).

Table 2 describes the administration details for each vaccine. Each vaccine will be administered as a 0.5-mL dose in the upper deltoid muscle of the left or right arm.

Table 2. Investigational Product Administration Schedule

Investigational Product	Group(s)	Visit(s)	Upper Deltoid Muscle Injection Location
Trumenba	2, 4, 6, and 8	1 and 3	Left arm
MenABCWY	1, 3, 5, and 7	1 and 3	Left arm
MenACWY-CRM	2, 4, 6, and 8	1	Right arm
Placebo	1, 3, 5, and 7	1	Right arm

6.1.2. Medical Devices

In this study, medical devices being used will be the vial adaptor for MenABCWY, as well as the PFSs for placebo and Trumenba.

Instructions for medical device use are provided in the IP manual.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the unblinded study personnel throughout the study.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

2. Investigational product will be shipped to the study site after required regulatory and legal documents have been received by the sponsor. These will be shipped at +2°C to +8°C. Upon receipt at the study site, the investigational product should be immediately transferred to a +2°C to +8°C temperature-monitored refrigerator for storage.

3. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

4. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record. Used needles and syringes should be disposed of according to local practice. Empty outer investigational product containers must be retained until reviewed by the sponsor's representative and then may be destroyed after the sponsor's representative has performed accountability. Investigational product return/destruction must be documented on the accountability log.

5. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.

6. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

7. Study interventions should be stored in their original containers and in accordance with the labels.

8. See the IP manual for storage conditions of the study intervention once reconstituted.

9. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

10. Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

11. The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an unblinded appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. The investigational product will be administered to participants who are blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

Allocation (randomization) of participants to vaccine groups will proceed through the use of an interactive response technology (IRT) system that is accessible 24 hours a day, 365 days a year. Having logged in, the site personnel (study coordinator or specified designee) will be required to enter or select certain information including but not limited to the user's identification (ID) and password, protocol number, the participant number, if the participant should be considered ACWY-naïve or -experienced, and the date of birth of the participant. The site personnel will then be provided with a participant randomization number and dispensable unit (DU) or container number. The randomization number and the date on which the randomization number was assigned will be recorded on the CRF. Once participant numbers, DU numbers, and randomization numbers have been assigned, they cannot be reassigned. The IRT system will provide a confirmation report containing the participant randomization number and DU or container number assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer-blinded study, the study staff dispensing, preparing, and administering the vaccine will be unblinded. All other study and site personnel, including the investigator, investigator staff, participants, and participants' parent(s)/legal guardian, will be blinded to investigational product assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the investigational products are different in physical appearance, the investigational product syringes will be administered in a manner that prevents the study participants from identifying the vaccine type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know investigational product assignments.

6.3.3. Blinding of the Sponsor

Those study team members who are involved in ensuring that protocol requirements for investigational product preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate). An unblinded clinician who is not a direct member of the study team will review unblinded protocol deviations. All other study team members and all laboratory testing personnel performing serology assays will remain blinded to vaccine assigned/received throughout the study. All laboratory testing personnel performing serology assays will also remain blinded to visit number throughout the study.

6.3.4. Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be either a manual or an electronic process. Blinding codes should only be broken in emergency situations for reasons of participant safety.

In case of an emergency, when knowledge of the investigational product assignment is required for the medical management of an individual participant, it may be unblinded. The investigator must notify a member of the study team immediately after determining that it is necessary to unblind the assignment. The investigator must also indicate in source documents that the blind was broken and provide the date and reason for breaking the blind. Any AE or SAE associated with breaking the blind must be recorded and reported as specified in this protocol.

6.4. Study Intervention Compliance

All doses of investigational product will be administered by the appropriately designated study staff at the investigator site.

6.5. Concomitant Therapy

The name and date of administration of any nonstudy vaccine (or allergen immunotherapy) given from the signing of the ICD up to Visit 4 (approximately 1 month after Vaccination 2) will be recorded on the CRF.

The name, start and stop dates, and route of administration for concomitant medications (prescription and nonprescription) used to treat an AE (excluding events recorded only in the e-diary) from the signing of the ICD to Visit 5 will be recorded in the CRF.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are women of childbearing potential (WOCBP) (see Appendix 4).

6.5.1. Prohibited During the Study

- Receipt of any blood products, including immunoglobulin.
- Nonstudy meningococcal vaccines.

- Nonlive or live nonstudy vaccines are not permitted 14 and 28 days, respectively, before or after any study vaccination (see exception below for any COVID-19 vaccination).

  Guidance provided by the US CDC states that COVID-19 vaccines and other vaccines may now be administered without regard to timing. Because of the COVID-19 pandemic and the ongoing COVID-19 vaccinations at the time of study recruitment, participants will be allowed to receive any authorized (nonexperimental) COVID-19 vaccination within 8 days of investigational product administration (ie, not permitted 7 days before or after any study vaccination).

- Intramuscular/sublingual allergen immunotherapy is not permitted within 14 days of any study vaccination.

- Systemic (oral, intravenous, or intramuscular) corticosteroid therapy within 28 days of any study vaccination.

6.5.2. Permitted During the Study

- Nonstudy vaccines used in the event of a disease outbreak or pandemic are allowed. However, while prioritizing standard clinical care, efforts should be made not to administer nonstudy vaccines within 14 days (for nonlive vaccines) or 28 days (for live vaccines) as specified below (see exception below for any COVID-19 vaccination).

  Guidance provided by the US CDC states that COVID-19 vaccines and other vaccines may now be administered without regard to timing. Because of the COVID-19 pandemic and the ongoing COVID-19 vaccinations at the time of study recruitment, participants will be allowed to receive any authorized (nonexperimental) COVID-19 vaccination within 8 days of investigational product administration (ie, not permitted 7 days before or after any study vaccination).

- Nonstudy vaccines (other than any meningococcal vaccines) that are part of recommended immunization schedules are allowed anytime during the study but should not be administered within 14 days (for nonlive vaccines) and 28 days (for live vaccines) of investigational product administration

- Antipyretic and other pain medication to treat symptoms following investigational product administration is permitted.

- A local anesthetic may be used at the site of the blood draw.

- Topical antibiotics are permitted.

- Topical and inhaled corticosteroids are permitted.

6.5.3. Prior Vaccinations and Treatments

If the participant is known to have ever received a polyribosylribitol phosphate oligosaccharide of *Haemophilus influenzae* type b conjugated to outer membrane protein (PRP-OMP) vaccine, the name of the vaccine and date of administration will be recorded on the CRF.

Only participants who have never received a prior dose, or who have received not more than 1 prior dose no sooner than 4 years prior to the date of randomization, of Menveo or Menactra may be enrolled (Section 5). If the participant has received any prior meningococcal vaccines or vaccines containing 1 or more ACWY groups, the trade name (if known) and date of administration will be recorded on the CRF. Please refer to the SRM for a list of ACWY-containing vaccines that are or have been commercially available. Written confirmation of vaccination history should be obtained prior to randomization.

6.5.4. Prohibited Prior Treatments

Receipt of any blood products, including immunoglobulin, within 6 months before the first study vaccination.

6.6. Dose Modification

Not applicable.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the institutional review board (IRB)/ethics committee (EC), or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of MenABCWY at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating participants and the hospital pharmacy (if applicable) immediately. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

At the time of discontinuing, please refer to the SRM and SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Participants should be questioned regarding their reason for withdrawal. The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

The participant should be requested to return for a final visit, if applicable, and the investigator will perform the procedures indicated for the next visit. Any AEs or SAEs that are continuing at the time of withdrawal from the study should be followed until resolution or, in case of permanent impairment, until the condition stabilizes.

A final telephone contact 6 months after the last vaccination Section 8.10.1.5 for the collection of safety information should be completed for all participants who withdraw or have been withdrawn after administration of investigational product, unless consent for further contact has been withdrawn, or the participant is lost to follow-up. Participant withdrawal should be explained in the source documents, and should include whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or postvaccination study follow-up.

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this the immunogenicity subset of this study is approximately 75 or 100 mL (depending on the amount of blood the participant has agreed to colled at Visit 4: 25 or 50 mL). The actual collection times of blood sampling may change.

8.1. Efficacy Assessments

Not applicable.

8.1.1. Immunogenicity Assessments

To facilitate immunogenicity analyses, participants in the immunogenicity subset will have approximately 25 mL of blood collected at Visit 1 (prior to Vaccination 1) and Visit 2 (1 month after Vaccination 1) and 25 or 50 mL of blood collected at Visit 4 (1 month after Vaccination 2). Sera obtained from participants at all time points will be used in these assays. LOD and LLOQ titers for these assays will be detailed in the statistical analysis plan (SAP). For participants ≥16 years of age who consent to providing an additional 25 mL (total 50 mL) of blood at Visit 4, the additional sera will be used for further assay development and validation and may be used to support current and ad hoc study endpoint immunogenicity analyses.

8.1.1.1. MenA, MenC, MenW, and MenY Serum Bactericidal Assays

For assessment of the immune response to MenACWY-CRM and the ACWY components of MenABCWY, test strains specific for each of the ACWY groups (A [PMB277], C [PMB3204], W [PMB6270], Y [PMB3385]) will be used in the hSBAs for determination of the immunogenicity endpoints in this study.

8.1.1.2. MenB Serum Bactericidal Assays

For assessment of the immune response to Trumenba and the B component of MenABCWY, 4 primary MenB test strains, PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44), will be used in the hSBAs for determination of the immunogenicity endpoints in this study.

8.1.2. Biological Samples

Blood samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's genetic material will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's genetic material is performed.

A mechanism (eg, appropriate wording within the study ICD) will be established that enables testing of serum samples obtained during the study to assess for the preexistence of select AEs reported during study participation.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Any participant who received at least 1 dose of investigational product will be included in the evaluation for safety. The following safety parameters will be assessed as described in the Study Procedures section (Section 8.10) and Section 1.3:

- Physical examination.
- Reactogenicity: solicited local reactions and systemic events, including fever.
- Use of antipyretic medication.
- Unsolicited AEs and SAEs.

A medical history will be obtained and a physical examination will be performed on all participants at Visit 1 to establish a baseline. When taking the medical history and performing the physical examination, particular care must be taken to note any neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Significant medical history and observations from the physical examination will be documented on the CRF. In addition, a urine pregnancy test will be performed on all female participants.

The safety parameters include reactogenicity, ie, both local reactions and systemic events that occur in the 7 days (Days 1 to 7) after investigational product administration. These prompted e-diary events are:

- Local reactions at the site of investigational product administration (redness, swelling, and pain).

- Systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain).

Local reactions, systemic events, and use of antipyretic medication associated with vaccine administration will be collected using an e-diary. For events that resolve after Day 7, the end date will be collected in the CRF. If a participant does not complete the e-diary for 7 days, end dates of local reactions, systemic events, or antipyretic medication use that were ongoing on the last day the e-diary was completed by the participant will be collected on the CRF.

Immediate AEs, defined as AEs occurring within the first 30 minutes after investigational product administration, will be assessed and documented on the AE CRF. The time of onset will be recorded for any AEs that occur on the same day as investigational product administration.

MAEs and NDCMCs will also be assessed throughout the study and documented on the appropriate AE CRF. An MAE is defined as a nonserious AE that results in an evaluation at a medical facility. An NDCMC is defined as a disease or medical condition, not previously identified, that is expected to be persistent or otherwise long-lasting in its effects.

AEs (serious and nonserious), NDCMCs, and visits to other medical facilities will be assessed at study visits as specified in the SoA and reported as defined in Section 8.3. AE-related hospitalizations, visits to other medical facilities, medication use, and days of school or work missed will be collected and recorded in the CRF. Hospitalizations and visits to medical facilities not associated with an AE, such as elective hospitalizations, healthcare visits for preventive care, or routine physical examinations, will not be collected. Non–AE-related concomitant medications and days of school or work missed not associated with an AE will not be collected. A Study Visit/Telephone Contact AE Checklist will be used as a guide, will be completed at each scheduled study visit/telephone contact, and will be included in the source documentation. Please refer to the SRM for details.

Participants will be given a memory aid at Visit 3. The memory aid will be used to remind participants to review any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility with study site personnel. Participants may use the memory aid as needed during the telephone contact at Visit 5 to prompt recall of events. These may be used to assist in reporting and discussion of events with study staff, but these memory aids will not be considered source documents and will not be collected at study visits. Only information collected by study staff as part of a study visit or telephone contact (Visit 5) will be included in the source documents and entered into the CRF.

In addition, AEs and SAEs will be collected as defined in Section 8.3.

8.2.1. Electronic Diary

An e-diary will be issued based on a personal digital assistant or equivalent technology, and used to monitor and record the participant's local reactions, systemic events, and use of antipyretic medication for 7 days after each vaccination. Grading scales for local reactions and systemic events are based on US Food and Drug Administration (FDA) Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.[14] The e-diary allows recording of these assessments only within a fixed time-window, thus providing the accurate representation of the participant's experience at that time.

For local reactions and systemic events that resolve after Day 7, the end date will be collected on the CRF. If the e-diary is not completed for 7 days, the end dates of local reactions, systemic events, or antipyretic medication use that occurred during the 7 days will be collected on the CRF. The investigator or designee should contact the parent(s)/legal guardian or participant in order to obtain stop dates for any solicited reactions or other solicited data ongoing on the last day that the e-diary was completed.

Data reported on the e-diary will be transferred electronically to the e-diary vendor (a trusted third party), where they will be available for review by investigators at all times via an internet-based portal. At intervals agreed upon between the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator on the CRF.

Investigators will be required to review the e-diary data online at frequent intervals to evaluate participant compliance and as part of the ongoing safety review.

8.2.1.1. Local Reactions

Local reactions (redness, swelling, and pain) at the site of investigational product administration will be recorded daily for 7 days (Days 1 to 7) after each vaccination. Only local reactions at the site of investigational product administration on the left arm will be recorded.

8.2.1.1.1. Redness and Swelling

Redness and swelling will be measured and recorded in caliper units (range: 1 to 21+), and then categorized as none, mild, moderate, or severe based on the scale given in Table 3. Each caliper unit represents 0.5 cm. A caliper will be issued with instructions for measuring any redness or swelling at the injection site. The caliper will be used to measure and to report the largest diameter of a local reaction. In the event that a caliper measurement is between 2 values, the higher value should be reported. The measurements will then be recorded in the e-diary.

In the event the reaction exceeds the maximum size the caliper is able to measure (>21 caliper units), the parent(s)/legal guardian or participant will also measure the maximum diameter of the redness and/or swelling at the injection site using the measuring tape/ruler provided and report this immediately to the investigator. The parent(s)/legal guardian or participant will report the maximum diameter of the redness and/or swelling at the injection site to the investigator daily until the reaction becomes ≤21 caliper units. These measurements will be recorded in the CRF.

Table 3. Grading of Redness and Swelling

None	0 to 2.0 cm (0 to 4 caliper units)
Mild	>2.0 to 5.0 cm (5 to 10 caliper units)
Moderate	>5.0 to 10.0 cm (11 to 20 caliper units)
Severe	>10.0 cm (>20 caliper units)

8.2.1.1.2. Pain

If the participant experiences injection site pain, the pain will be graded using the scale in Table 4. The assessment will then be recorded in the e-diary.

Table 4. Grading of Pain

Mild	Does not interfere with activity
Moderate	Interferes with activity
Severe	Prevents daily activity

8.2.1.2. Systemic Events

8.2.1.2.1. Temperature

A digital thermometer will be given to the parent(s)/legal guardian or the participant with instructions on how to measure the participant's oral temperature at home. Oral temperature will be collected at in the evening daily for 7 days (Day 1 to Day 7) after each vaccination, and at any time during the 7 days when fever is suspected. The highest temperature for each day will be recorded in the e-diary. Fever is defined as temperature of ≥38.0°C (100.4°F).

Temperature will be measured and recorded to 1 decimal place and then categorized according to the severity scale in Table 5.

Table 5. Severity Scale for Fever

Temperature 38.0°C to 38.4°C (100.4°F to 101.1°F)
Temperature 38.5°C to 38.9°C (101.2°F to 102.0°F)
Temperature 39.0°C to 40.0°C (102.1°F to 104.0°F)
Temperature >40.0°C (>104.0°F)

8.2.1.2.2. Other Systemic Events

The e-diary will be used to record the presence of other systemic events, including vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at the injection site, and joint pain daily for 7 days (Day 1 to Day 7) after each vaccination, using the scales in Table 6.

Table 6. Grading of Other Systemic Events

	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires IV hydration
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Fatigue	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Muscle pain (other than muscle pain at the injection site)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity

Abbreviation: IV = intravenous.

8.2.1.2.3. Use of Antipyretic Medication

The use of antipyretic medication will be recorded in the e-diary daily during the active safety observation periods (Day 1 to Day 7) for each vaccination.

8.2.2. Pregnancy Testing

Urine pregnancy tests will have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of the vaccine. A negative pregnancy test result will be required prior to the participant's receiving the investigational product. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations.

In the case of a positive confirmed pregnancy at Visit 1, the participant will not be eligible for participation.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or caused the participant to discontinue from the study (see Section 7).

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant/parent(s)/legal guardian begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including Visit 4. At Visit 5, the participant will be contacted by telephone to inquire about SAEs, MAEs, and NDCMCs, since Visit 4.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.

Follow-up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the Vaccine SAE Reporting Form immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until the end of study participation.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the Vaccine SAE Reporting Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the Vaccine SAE Reporting Form, regardless of whether there is an associated SAE. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the investigator site file.

8.3.6. Medical Device Incidents (Including Malfunctions)

Medical devices are being provided for use in this study for the purposes of administering and preparing investigational product. In order to fulfill regulatory reporting obligations worldwide, the unblinded site staff is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a medical device incident can be found in Appendix 6.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 3 of the protocol.

8.3.6.1. Time Period for Detecting Medical Device Incidents

Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device incidents is provided in Appendix 6.

8.3.6.2. Follow-up of Medical Device Incidents

All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3.3). This applies to all participants, including those who discontinue study intervention.

The unblinded site staff are responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the unblinded site staff.

8.3.6.3. Prompt Reporting of Medical Device Incidents to Sponsor

Medical device incidents will be reported to the sponsor within 24 hours after the unblinded site staff determines that the event meets the protocol definition of a medical device incident.

Information will be provided to the sponsor as described in the IP manual.

The same individual will be the contact for the receipt of medical device reports and SAEs.

8.3.6.4. Regulatory Reporting Requirements for Medical Device Incidents

The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/EC.

8.3.7. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	**Recorded on the CRF**	**Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness**
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Other examples include, but are not limited to:

- The administration of expired investigational product;
- The administration of an incorrect investigational product;
- The administration of an incorrect dosage;
- The administration of investigational product that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the investigational product under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Reporting Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of investigational product greater than 1 dose of investigational product within a 24-hour time period will be considered an overdose. Pfizer does not recommend specific treatment for an overdose. In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.

2. Closely monitor the participant for any AEs/SAEs.

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Not applicable.

8.6. Pharmacodynamics

Not applicable.

8.7. Genetics

Not applicable.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.10. Study Procedures

8.10.1. Group 1-4 Participants - Immunogenicity Subset

8.10.1.1. Visit 1 (Day 1): Vaccination 1

In the case of temporary delay of vaccination, procedures and assessments below will be redone or reconfirmed, as applicable, on the day of vaccination.

- Obtain written informed consent, and assent if appropriate, before performing study-specific procedures. The date of informed consent will be recorded on the CRF.

- Record the participant's demographic information (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

- Record the presence of chronic conditions and/or medical history of significance, including relevant surgical procedures and cardiac medical history.

- Record previous PRP-OMP vaccinations as described in the Prior Vaccinations and Treatments section (Section 6.5.3).

- Record any prior meningococcal vaccines or vaccines containing 1 or more ACWY groups as described in the Prior Vaccinations and Treatments section (Section 6.5.3).

- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, throat; heart; lungs; abdomen; extremities; neurological; musculoskeletal; and lymph nodes; including worsening of medical history conditions. Results must be recorded on source documents and the CRF. Findings from a physical examination conducted as part of standard routine care and before informed consent may be used for purposes of the study only if the examination was performed no more than 2 days before vaccination. A brief examination must be performed on the day of vaccination to document that no change in health has occurred in the interim.

- On the day of vaccination, perform a urine pregnancy test on female participants. A negative pregnancy test result is required before the participant may receive the investigational product.

- On the day of and before vaccination, measure and record the participant's oral temperature.

- Ensure that all of the inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met.

- If a participant is eligible for the study, randomize the participant using an interactive voice response system (IVRS), interactive Web-based response system (IWRS), or an equivalent system.

- On the day of and before vaccination, collect a blood sample (approximately 25 mL). Collect the blood sample only if the participant is eligible for vaccination on the same day.

- The unblinded administrator administers a single 0.5-mL intramuscular injection of either MenABCWY (Groups 1 and 3) or Trumenba (Groups 2 and 4) into the upper deltoid muscle of the left arm; and either MenACWY-CRM (Groups 2 and 4) or saline (Groups 1 and 3) into the upper deltoid muscle of the right arm. The time of investigational product administration will be recorded on the CRF.

- Observe the participant for at least 30 minutes (or longer as per local practice) after the investigational product administration for any acute reactions. Record any AEs observed during the 30-minute observation period; these AEs are defined as immediate AEs (Section 8.2).

- Record AEs as described in the AE reporting requirements section (Section 8.3) and the SoA. Time of onset will be recorded for any AEs that occur on the same day as investigational product administration.

- Record concomitant medications used to treat AEs as described in the Concomitant Therapy section (Section 6.5).

- Issue a participant e-diary and provide instruction on its completion. Ask the parent(s)/legal guardian or participant to complete the e-diary from Day 1 to Day 7 after vaccination. Day 1 is the day of vaccination.

- Issue a caliper, a measuring tape/ruler, and a digital thermometer and provide instructions on their use.

- Measuring tape/ruler data must be collected by the parent(s)/legal guardian for minor participants. All data must be recorded in the e-diary by the parent(s)/legal guardian for minor participants.

- Ask the parent(s)/legal guardian or the participant to use the caliper to measure the maximum diameter of redness and swelling at the left arm injection site each day for the 7 days after study vaccination and record in the e-diary as described in Section 8.2.1.1.1.

- Ask the parent(s)/legal guardian or the participant to contact the investigator immediately if the participant experiences severe redness or swelling (>20 caliper units) at the left arm injection site, a fever ≥39.0°C (102.1°F), or a severe headache within 7 days after vaccination, as an unscheduled visit should be arranged (Section 8.11).

- If the reaction exceeds the maximum size the caliper is able to measure (>21 caliper units), the parent(s)/legal guardian or the participant should also use the measuring tape/ruler to measure the maximum diameter of redness and/or swelling at the injection site, and report this immediately to the investigator.

- Ask the parent(s)/legal guardian or participant to report the maximum diameter of the redness and/or swelling at the injection site to the investigator daily until the reaction becomes ≤21 caliper units.

- Provide the parent(s)/legal guardian or participant with a contact card (Section 10.1.10).

- Ask the parent(s)/legal guardian or the participant to contact the investigator immediately if any significant illness or hospitalization occurs.

- Schedule an appointment for the next study visit and confirm that it is scheduled within the time window per protocol.
- Remind the parent(s)/legal guardian or participant to bring the e-diary to the next study visit.
- Complete the source documents.
- Complete the CRF and update the investigational product accountability records.

Between visits, review the e-diary data online at frequent intervals. Contact the parent(s)/legal guardian or the participant to obtain stop dates for any local reactions, systemic events, or use of antipyretic medication that were ongoing on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered into the CRF at the next study visit of the participant.

8.10.1.2. Visit 2 (28 to 42 Days After Visit 1), Post–Vaccination 1 Blood Draw

- Ensure that the participant continues to be eligible for the study, and continues to comply with contraception requirements detailed in Section 5.
- Ensure that the participant continues to meet none of the withdrawal criteria and none of the temporary delay of blood draw criteria as described in Section 5.2.1.
- Collect the participant's e-diary.
- Review the participant's e-diary data since the previous visit and follow up on any ongoing reactogenicity or use of antipyretic medication.
- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the SRM for additional details.
    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.
- Record AEs as described in the AE reporting requirements section (Section 8.3) and the SoA.
- Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.

- Record nonstudy vaccinations as described in the Concomitant Therapy section (Section 6.5).
- Record concomitant medications used to treat AEs as described in the Concomitant Therapy section (Section 6.5).
- Collect a blood sample (approximately 25 mL).
- Ask the parent(s)/legal guardian or the participant to contact the investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the next visit and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.
- Complete the CRFs.

8.10.1.3. Visit 3 (173 to 194 Days After Visit 1): Vaccination 2

In the case of temporary delay of vaccination, procedures and assessments below will be redone or reconfirmed, as applicable, on the day of vaccination.

- Ensure that the participant continues to be eligible for the study, and continues to comply with contraception requirements detailed in Section 5.
- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 5.2.1 and none of the temporary delay of vaccination or blood draw criteria as described in Section 5.2.1.
- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the SRM for additional details.
    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.
- Record AEs as described in the AE reporting requirements section (Section 8.3) and the SoA. Time of onset will be recorded for any AEs that occur on the same day as investigational product administration.
- Review AEs that were ongoing from the previous visit and record their end dates or confirm that they are still continuing.

- Record nonstudy vaccinations as described in the Concomitant Therapy section (Section 6.5).

- Record concomitant medications used to treat AEs as described in the Concomitant Therapy section (Section 6.5).

- On the day of vaccination, perform a urine pregnancy test on female participants. A negative pregnancy test result is required before the participant may receive the investigational product.

- On the day of and before vaccination, measure and record the participant's oral temperature.

- The unblinded administrator administers a single 0.5-mL intramuscular injection of either MenABCWY (Groups 1 and 3) or Trumenba (Groups 2 and 4) into the upper deltoid muscle of the left arm. The time of investigational product administration will be recorded on the CRF.

- Observe the participant for at least 30 minutes (or longer as per local practice) after the investigational product administration for any acute reactions. Record any AEs observed during the 30-minute observation period; these AEs are defined as immediate AEs (Section 8.2).

- Issue a participant e-diary and provide instruction on its completion. Ask the parent(s)/legal guardian or participant to complete the e-diary from Day 1 to Day 7 after vaccination. Day 1 is the day of vaccination.

- Issue a caliper, a measuring tape/ruler, and a digital thermometer and provide instructions on their use.

- Measuring tape/ruler data must be collected by the parent(s)/legal guardian for minor participants. All data must be recorded in the e-diary by the parent/legal guardian for minor participants.

- Ask the parent(s)/legal guardian or the participant to use the caliper to measure the maximum diameter of redness and swelling at the left arm injection site each day for the 7 days after study vaccination and record in the e-diary as described in Section 8.2.1.1.1.

- Ask the parent(s)/legal guardian or the participant to contact the investigator immediately if the participant experiences a severe redness or swelling (>20 caliper units) at the left arm injection site, a fever ≥39.0°C (102.1°F), or a severe headache within 7 days after vaccination, as an unscheduled visit should be arranged (Section 8.11).

- If the reaction exceeds the maximum size the caliper is able to measure (>21 caliper units), the parent/legal guardian or the participant should also use the measuring tape/ruler to measure the maximum diameter of redness and/or swelling at the injection site, and report this immediately to the investigator.

- Ask the parent(s)/legal guardian or participant to report the maximum diameter of the redness and/or swelling at the injection site to the investigator daily until the reaction becomes ≤21 caliper units.

- Provide the parent(s)/legal guardian or the participant with a memory aid. Instruct the participant to use the memory aid between Visits 4 and 5 to remind him or her to review any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility with study site personnel. The memory aid is not a diary for the collection of reactogenicity. Please refer to the SRM for additional details.

- Ask the parent(s)/legal guardian or the participant to contact the investigator immediately if any significant illness or hospitalization occurs.

- Schedule an appointment for the next study visit and confirm that it is scheduled within the time window per protocol.

- Ask the parent(s)/legal guardian or the participant to bring the e-diary to the next visit.

- Complete the source documents.

- Complete the CRF and update the investigational product accountability records.

Between visits, review the e-diary data online at frequent intervals. Contact the parent(s)/legal guardian or the participant to obtain stop dates for any local reactions, systemic events, or use of antipyretic medication that were ongoing on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered into the CRF at the next study visit of the participant.

8.10.1.4. Visit 4 (28 to 42 Days After Visit 3), Post–Vaccination 2 Blood Draw

- Ensure that the participant continues to be eligible for the study, and continues to comply with contraception requirements detailed in Section 5.

- Ensure that the participant continues to meet none of the withdrawal criteria and none of the temporary delay of blood draw criteria as described in Section 5.2.1.

- Collect the participant's e-diary.

- Review the participant's e-diary data since the previous visit and follow up on any ongoing reactogenicity or use of antipyretic medication.

- Complete the Study Visit/Telephone Contact AE Checklist to:
  - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the SRM for additional details.
  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.
- Record AEs as described in the AE reporting requirements section (Section 8.3) and the SoA.
- Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Record nonstudy vaccinations as described in the Concomitant Therapy section (Section 6.5).
- Record concomitant medications used to treat AEs as described in the Concomitant Therapy section (Section 6.5).
- Collect a blood sample (approximately 25 mL [or 50 mL for the subset of consented participants ≥16 years of age]).
- Ask the parent(s)/legal guardian or the participant to contact the investigator immediately if any significant illness or hospitalization occurs.
- Schedule a telephone contact and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.
- Complete the CRFs.

8.10.1.5. Visit 5 (168 to 196 Days After Last Vaccination), Telephone Contact

- This telephone contact should occur approximately 6 months after the last study vaccination; this contact should be attempted for all participants who have received at least 1 study vaccination, unless they have withdrawn consent.
- Contact the parent(s)/legal guardian or the participant by telephone.

- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire about SAEs, NDCMCs, or AEs that resulted in evaluation at a medical facility since the last visit. Please refer to the SRM for additional details.
    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. A checklist will be provided as a guide. Please refer to the SRM for additional details.
- Report any SAEs to the sponsor as defined in Section 8.3.
- Record AEs as described in the AE reporting requirements section (Section 8.3) and the SoA.
- Record concomitant medications used to treat AEs as described in the Concomitant Therapy Section 6.5.
- Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Complete the source documents.
- Complete the CRFs.

8.10.2. Group 5-8 Participants - Safety Subset

8.10.2.1. Visit 1 (Day 1): Vaccination 1

In the case of temporary delay of vaccination, procedures and assessments below will be redone or reconfirmed, as applicable, on the day of vaccination.

- Obtain written informed consent, and assent if appropriate, before performing study-specific procedures. The date of informed consent will be recorded on the CRF.
- Record the participant's demographic information (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Record the presence of chronic conditions and/or medical history of significance, including relevant surgical procedures and cardiac medical history.
- Record previous PRP-OMP vaccinations as described in the Prior Vaccinations and Treatments section (Section 6.5.3).
- Record any prior meningococcal vaccines or vaccines containing 1 or more ACWY groups as described in the Prior Vaccinations and Treatments section (Section 6.5.3).

- Perform physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, throat; heart; lungs; abdomen; extremities; neurological; musculoskeletal; and lymph nodes; including worsening of medical history conditions. Results must be recorded on source documents and the CRF. Findings from a physical examination conducted as part of standard routine care and before informed consent may be used for purposes of the study only if the examination was performed no more than 2 days before vaccination. A brief examination must be performed on the day of vaccination to document that no change in health has occurred in the interim.

- On the day of vaccination, perform a urine pregnancy test on female participants. A negative pregnancy test result is required before the participant may receive the investigational product.

- On the day of and before vaccination, measure and record the participant's oral temperature.

- Ensure that all of the inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met.

- If a participant is eligible for the study, randomize the participant using an IVRS, IWRS, or an equivalent system.

- The unblinded administrator administers a single 0.5-mL intramuscular injection of either MenABCWY (Groups 5 and 7) or Trumenba (Groups 6 and 8) into the upper deltoid muscle of the left arm; and either MenACWY-CRM (Groups 6 and 8) or saline (Groups 5 and 7) into the upper deltoid muscle of the right arm. The time of investigational product administration will be recorded on the CRF.

- Observe the participant for at least 30 minutes (or longer as per local practice) after the investigational product administration for any acute reactions. Record any AEs observed during the 30-minute observation period; these AEs are defined as immediate AEs (Section 8.2).

- Record AEs as described in the AE reporting requirements section (Section 8.3) and the SoA. Time of onset will be recorded for any AEs that occur on the same day as investigational product administration.

- Record concomitant medications used to treat AEs as described in the Concomitant Therapy section (Section 6.5).

- Issue a participant e-diary and provide instruction on its completion. Ask the parent(s)/legal guardian or participant to complete the e-diary from Day 1 to Day 7 after vaccination. Day 1 is the day of vaccination.

- Issue a caliper, a measuring tape/ruler, and a digital thermometer and provide instructions on their use.

- Measuring tape/ruler data must be collected by the parent(s)/legal guardian for minor participants. All data must be recorded in the e-diary by the parent(s)/legal guardian for minor participants.

- Ask the parent(s)/legal guardian or the participant to use the caliper to measure the maximum diameter of redness and swelling at the left arm injection site each day for the 7 days after study vaccination and record in the e-diary as described in Section 8.2.1.1.1.

- Ask the parent(s)/legal guardian or the participant to contact the investigator immediately if the participant experiences severe redness or swelling (>20 caliper units) at the left arm injection site, a fever ≥39.0°C (102.1°F), or a severe headache within 7 days after vaccination, as an unscheduled visit should be arranged (Section 8.11).

- If the reaction exceeds the maximum size the caliper is able to measure (>21 caliper units), the parent(s)/legal guardian or the participant should also use the measuring tape/ruler to measure the maximum diameter of redness and/or swelling at the injection site, and report this immediately to the investigator.

- Ask the parent(s)/legal guardian or participant to report the maximum diameter of the redness and/or swelling at the injection site to the investigator daily until the reaction becomes ≤21 caliper units.

- Provide the parent(s)/legal guardian or participant with a contact card (Section 10.1.10).

- Ask the parent(s)/legal guardian or the participant to contact the investigator immediately if any significant illness or hospitalization occurs.

- Schedule an appointment for the next study visit and confirm that it is scheduled within the time window per protocol.

- Remind the parent(s)/legal guardian or participant to bring the e-diary to the next study visit.

- Complete the source documents.

- Complete the CRF and update the investigational product accountability records.

Between visits, review the e-diary data online at frequent intervals. Contact the parent(s)/legal guardian or the participant to obtain stop dates for any local reactions, systemic events, or use of antipyretic medication that were ongoing on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered into the CRF at the next study visit of the participant.

8.10.2.2. Visit 2 (28 to 42 Days After Visit 1), Post–Vaccination 1 Telephone Contact

- Visit 2 will be a telephone contact for participant in the safety subset (Groups 5-8).
- Ensure that the participant continues to be eligible for the study, and continues to comply with contraception requirements detailed in Section 5.
- Ensure that the participant continues to meet none of the withdrawal criteria and none of the temporary delay of blood draw criteria as described in Section 5.2.1.
- Review the participant's e-diary data since the previous visit and follow up on any ongoing reactogenicity or use of antipyretic medication.
- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the SRM for additional details.
    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.
- Record AEs as described in the AE reporting requirements section (Section 8.3) and the SoA.
- Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Record nonstudy vaccinations as described in the Concomitant Therapy section (Section 6.5).
- Record concomitant medications used to treat AEs as described in the Concomitant Therapy section (Section 6.5).
- Ask the parent(s)/legal guardian or the participant to contact the investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the next visit and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.
- Complete the CRFs.

8.10.2.3. Visit 3 (173 to 194 Days After Visit 1): Vaccination 2

In the case of temporary delay of vaccination, procedures and assessments below will be redone or reconfirmed, as applicable, on the day of vaccination.

- Ensure that the participant continues to be eligible for the study, and continues to comply with contraception requirements detailed in Section 5.
- Ensure that the participant continues to meet none of the withdrawal criteria as described in Section 5.2.1 and none of the temporary delay of vaccination or blood draw criteria as described in Section 5.2.1.
- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the SRM for additional details.
    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.
- Record AEs as described in the AE reporting requirements section (Section 8.3) and the SoA. Time of onset will be recorded for any AEs that occur on the same day as investigational product administration.
- Review AEs that were ongoing from the previous visit and record their end dates or confirm that they are still continuing.
- Record nonstudy vaccinations as described in the Concomitant Therapy section (Section 6.5).
- Record concomitant medications used to treat AEs as described in the Concomitant Therapy section (Section 6.5).
- On the day of vaccination, perform a urine pregnancy test on female participants. A negative pregnancy test result is required before the participant may receive the investigational product.
- On the day of and before vaccination, measure and record the participant's oral temperature.
- The unblinded administrator administers a single 0.5-mL intramuscular injection of either MenABCWY (Groups 5 and 7) or Trumenba (Groups 6 and 8) into the upper deltoid muscle of the left arm. The time of investigational product administration will be recorded on the CRF.

- Observe the participant for at least 30 minutes (or longer as per local practice) after the investigational product administration for any acute reactions. Record any AEs observed during the 30-minute observation period; these AEs are defined as immediate AEs (Section 8.2).

- Issue a participant e-diary and provide instruction on its completion. Ask the parent(s)/legal guardian or participant to complete the e-diary from Day 1 to Day 7 after vaccination. Day 1 is the day of vaccination.

- Issue a caliper, a measuring tape/ruler, and a digital thermometer and provide instructions on their use.

- Measuring tape/ruler data must be collected by the parent(s)/legal guardian for minor participants. All data must be recorded in the e-diary by the parent/legal guardian for minor participants.

- Ask the parent(s)/legal guardian or the participant to use the caliper to measure the maximum diameter of redness and swelling at the left arm injection site each day for the 7 days after study vaccination and record in the e-diary as described in Section 8.2.1.1.1.

- Ask the parent(s)/legal guardian or the participant to contact the investigator immediately if the participant experiences a severe redness or swelling (>20 caliper units) at the left arm injection site, a fever ≥39.0°C (102.1°F), or a severe headache within 7 days after vaccination, as an unscheduled visit should be arranged (Section 8.11).

- If the reaction exceeds the maximum size the caliper is able to measure (>21 caliper units), the parent/legal guardian or the participant should also use the measuring tape/ruler to measure the maximum diameter of redness and/or swelling at the injection site, and report this immediately to the investigator.

- Ask the parent(s)/legal guardian or participant to report the maximum diameter of the redness and/or swelling at the injection site to the investigator daily until the reaction becomes ≤21 caliper units.

- As detailed in the SRM, provide the participant with instructions and materials for returning the e-diary to the investigational site after completion.

- Provide the parent(s)/legal guardian or the participant with a memory aid. Instruct the participant to use the memory aid between Visits 4 and 5 to remind him or her to review any significant illnesses, hospitalizations, NDCMCs, or visits to a medical facility with study site personnel. The memory aid is not a diary for the collection of reactogenicity. Please refer to the SRM for additional details.

- Ask the parent(s)/legal guardian or the participant to contact the investigator immediately if any significant illness or hospitalization occurs.

- Schedule an appointment for the next study visit and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.
- Complete the CRF and update the investigational product accountability records.

Between visits, review the e-diary data online at frequent intervals. Contact the parent(s)/legal guardian or the participant to obtain stop dates for any local reactions, systemic events, or use of antipyretic medication that were ongoing on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered into the CRF at the next study visit of the participant.

8.10.2.4. Visit 4 (28 to 42 Days After Visit 3), Post–Vaccination 2 Telephone Contact

- Visit 4 will be a telephone contact for participants in the safety subset (Groups 5-8).
- Ensure that the participant continues to be eligible for the study, and continues to comply with contraception requirements detailed in Section 5.
- Ensure that the participant continues to meet none of the withdrawal criteria and none of the temporary delay of blood draw criteria as described in Section 5.2.1.
- Review the participant's e-diary data since the previous visit and follow up on any ongoing reactogenicity or use of antipyretic medication.
- Complete the Study Visit/Telephone Contact AE Checklist to:
  - Inquire whether the participant had any NDCMCs since the last visit. Inquire whether the participant had any of the following related to an AE since the last visit: hospitalizations, visits to other medical facilities, medication use, or missed days of school or work. Please refer to the SRM for additional details.
  - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. Please refer to the SRM for additional details.
- Record AEs as described in the AE reporting requirements section (Section 8.3) and the SoA.
- Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Record nonstudy vaccinations as described in the Concomitant Therapy section (Section 6.5).

- Record concomitant medications used to treat AEs as described in the Concomitant Therapy section (Section 6.5).
- Ask the parent(s)/legal guardian or the participant to contact the investigator immediately if any significant illness or hospitalization occurs.
- Schedule a telephone contact and confirm that it is scheduled within the time window per protocol.
- Complete the source documents.
- Complete the CRFs.

8.10.2.5. Visit 5 (168 to 196 Days After Last Vaccination), Telephone Contact

- This telephone contact should occur approximately 6 months after the last study vaccination; this contact should be attempted for all participants who have received at least 1 study vaccination, unless they have withdrawn consent.
- Contact the parent(s)/legal guardian or the participant by telephone.
- Complete the Study Visit/Telephone Contact AE Checklist to:
    - Inquire about SAEs, NDCMCs, or AEs that resulted in evaluation at a medical facility since the last visit. Please refer to the SRM for additional details.
    - Inquire about neuroinflammatory and autoimmune conditions, such as transverse myelitis, uveitis, optic neuritis, and multiple sclerosis. A checklist will be provided as a guide. Please refer to the SRM for additional details.
- Report any SAEs to the sponsor as defined in Section 8.3.
- Record AEs as described in the AE reporting requirements section (Section 8.3) and the SoA.
- Record concomitant medications used to treat AEs as described in the Concomitant Therapy Section 6.5.
- Review AEs that were ongoing since the previous visit and record their end dates or confirm that they are still continuing.
- Complete the source documents.
- Complete the CRFs.

8.11. Unscheduled Visits

If the participant experiences a severe redness or swelling at the left arm injection site (>20 caliper units), a temperature ≥39.0°C (102.1°F), or a severe headache in the 7 days after vaccination, a study site visit should be arranged as soon as possible to assess the extent of the event. The parent(s)/legal guardian or participant contact will be documented in the CRF.

If the reaction exceeds the maximum size the caliper is able to measure (>21 caliper units, Section 8.2.1.1.1), ensure the parent(s)/legal guardian or participant has also measured the maximum diameter of the redness and/or swelling at the injection site using the measuring tape/ruler provided. Ask the parent(s)/legal guardian or participant to report the maximum diameter of the redness and/or swelling at the injection site daily until the reaction becomes ≤21 caliper units. Record these measurements in the CRF.

At an unscheduled visit, the participant's oral temperature should be measured and the symptom that prompted the visit should be assessed by a medically qualified member of the study staff. Findings will be recorded on the CRF. If the participant experiences any unsolicited AEs, these should be recorded on the AE CRF.

If the unscheduled visit does not take place following participant report of fever ≥39.0°C, severe redness/swelling, or severe headache, the reason must be documented in the CRF (for example, reaction no longer present or e-diary entry error).

For the purpose of assessments performed during unscheduled visits, a medically qualified member of the study staff is a study physician or a study nurse, as applicable to the investigator's local practice.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimands corresponding to each primary, secondary, and tertiary/exploratory objective are described in the table in Section 3. For estimands to evaluate the immunogenicity objectives for noninferiority, these estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. This addresses the objective of estimating the maximum potential difference between 2 groups, since the impact of noncompliance is likely to diminish the observed difference between the 2 groups. The mechanism for missing data is assumed to be missing completely at random (MCAR), and missing serology results will not be imputed.

In the primary safety objective evaluations, missing e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules.

9.1.2. Statistical Hypotheses

This study has 2 primary objectives and 1 secondary objective where hypothesis testing is applicable. The primary objectives are 1) to demonstrate that the immune response induced by 2 doses of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM, for ACWY-naïve and ACWY-experienced participants separately and 2) to demonstrate that the immune response for MenB induced by 2 doses of MenABCWY is noninferior to the immune response induced by 2 doses of Trumenba. The hypothesis testing for the secondary objective is to demonstrate that the immune response induced by 1 dose of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM, for ACWY-naïve and ACWY-experienced participants separately. Hypothesis testing for the secondary objective will be performed only if the primary objectives are successful.

For all objectives evaluating noninferiority of the immune response for MenA, MenC, MenW, and MenY, the definition of a seroresponder is a participant achieving at least a 4-fold rise in hSBA titer from baseline for each ACWY test strain, at the relevant analysis time point.

For the ACWY noninferiority evaluation in ACWY-naïve participants, the immune response will be evaluated at 1 month following Vaccination 2 for Group 1 and at 1 month following Vaccination 1 for Group 2. The null hypothesis (H_0) for each ACWY serogroup for noninferiority is as follows:

H_0: $\pi_{G1} - \pi_{G2} \leq -10\%$

where π_{G1} and π_{G2} are the percentages of participants who achieve a 4-fold rise in hSBA titers for MenA, MenC, MenW, and MenY for Group 1 and Group 2, respectively.

If the lower limit of the 2-sided 95% confidence interval (CI) for the difference in seroresponders (Group 1 – Group 2) is > -10% for all of the ACWY test strains (at 1 month after the second vaccination for Group 1 and at 1 month after the first vaccination for Group 2), the noninferiority of the MenABCWY regimen to the MenACWY-CRM regimen is declared for the ACWY-naïve participants.

For the ACWY noninferiority evaluation in ACWY-experienced participants, the approach will be identical to in ACWY-naïve participants, but Group 3 will be compared to Group 4, instead of Group 1 compared to Group 2. The noninferiority evaluations for both the ACWY-naïve and the ACWY-experienced participants are required to be successful to meet the first primary objective.

The second primary objective will be evaluated at 1 month following Vaccination 2 and the post–Vaccination 2 evaluable population will be used. The null hypothesis (H_0) for noninferiority for each primary MenB test strain is as follows:

H_0: $\pi_{G1+G3} - \pi_{G2+G4} \leq -10\%$

where π_{G1+G3} and π_{G2+G4} are the percentages of 4-fold rises and composite responses for Groups 1 and 3 combined and for Groups 2 and 4 combined, respectively, at 1 month after the second vaccination.

If the lower limit of the 2-sided 95% CI for the differences in 4-fold rises and composite responses (Group 1+3 – Group 2+4) is > -10% for all of the primary MenB test strains at 1 month after the second vaccination, the noninferiority of the MenABCWY regimen to the Trumenba regimen is declared.

If noninferiority for both the primary objectives is demonstrated, then an additional noninferiority evaluation of the ACWY response will be performed. This evaluation will be a secondary objective and will be conducted as for the primary ACWY noninferiority assessment; however, the secondary objective will be an evaluation of noninferiority of seroresponders who achieve a 4-fold rise at 1 month following Vaccination 1 for both groups evaluated (Group 1 versus Group 2 for ACWY-naïve and Group 3 versus Group 4 for ACWY-experienced).

9.1.3. Multiplicity Considerations

All the primary immunogenicity endpoints/estimands are considered coprimary in the study. For the primary immunogenicity objectives comparing immune responses induced by vaccine antigens from the MenABCWY group(s) to that from the comparator group(s), noninferiority is assessed by hypothesis tests as stated in Section 9.1.2, at a 2-sided level of 0.05 for each of the endpoints. The primary immunogenicity objectives will be met if noninferiority is achieved for each endpoint. Therefore, the type I error rate for the immunogenicity assessment is well controlled at the 0.05 level. If the primary objectives are met, then testing of noninferiority for all the secondary endpoints related to seroresponders who achieve a 4-fold rise at 1 month after Vaccination 1 will be done at the 0.05 level.

9.2. Sample Size Determination

9.2.1. Immunogenicity Subset (Groups 1-4)

Table 7 and Table 8 present the power to demonstrate that the immune response induced by 2 doses of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM for ACWY-naïve and ACWY-experienced participants, respectively, and Table 9 presents the power to demonstrate that the immune response induced by 2 doses of MenABCWY is noninferior to the immune response induced by 2 doses of Trumenba. The study is powered based on a combined (product) power across both the primary objectives.

Noninferiority comparisons will be based on the 4-fold rises and also composite response for the MenB endpoints (at 1 month following Vaccination 2) and seroresponders who achieve a 4-fold response for the ACWY endpoints (at 1 month after Vaccination 2 for Groups 1 and 3 and at 1 month after Vaccination 1 for Groups 2 and 4). The lower bounds of the corresponding 95% CIs of the group differences will be compared to the noninferiority criterion (-10%).

With 360, 180, 540, and 270 evaluable participants in Groups 1, 2, 3, and 4, respectively, and the assumptions in the tables below, the power is:

- above 99.9% to demonstrate noninferiority for the first primary objective relating to the ACWY response in ACWY-naïve participants,
- above 99.4% to demonstrate noninferiority for the first primary objective relating to the ACWY response in ACWY-experienced participants, and
- above 91.6% for the second primary objective relating to the MenB response.

The combined power, across both primary objectives, is above 91.0%. Therefore, assuming a nonevaluable rate of 20%, 450, 225, 675, and 338 participants in Groups 1, 2, 3, and 4, respectively, will be enrolled to have sufficient evaluable participants.

Some participants may be moved from the safety subset to the immunogenicity subset as described in Section 4.1. The sponsor may decide to proceed with less than full enrollment if an assessment of power shows that it is sufficient (<91% with full enrollment but still >85%) to meet the primary objectives. This assessment will be done in a completely blinded fashion before any participants are unblinded or the immunogenicity data are accessed.

Table 7. Power Analysis for First Primary Immunogenicity Objective (ACWY-Naïve Participants)

Criteria	ACWY Test Strains	Reference Rate (Group 2)[a]	Assumed Difference (G1 – G2)[a]	Number of Evaluable Participants (Group 1)	Number of Evaluable Participants (Group 2)	Power[b]	Power to Meet NI for All Serogroups
Lower limit of 95% CI for the difference in seroresponders (Group 1 – Group 2) > -10%	MenA	95.8%	0	360	180	99.96%	
	MenC	70%	15%	360	180	>99.99%	
	MenW	75.9%	15%	360	180	>99.99%	
	MenY	71.9%	15%	360	180	>99.99%	
						Power (to meet NI for all ACWY test strains)	>99.93%

Abbreviations: ACWY = meningococcal groups A, C, W, and Y; G1 and G2 = Groups 1 and 2; MenA, MenC, MenW, and MenY = *Neisseria meningitidis* groups A, C, W, and Y; NI = noninferiority.
a. Reference Study B1971057, ACWY-naïve participants.
b. At 0.05 alpha level (2-sided).

Table 8. Power Analysis for First Primary Immunogenicity Objective (ACWY-Experienced Participants)

Criteria	ACWY Test Strains	Reference Rate (Group 3)[a]	Assumed Difference (G3 – G4)[a]	Number of Evaluable Participants (Group 3)	Number of Evaluable Participants (Group 4)	Power[b]	Power to Meet NI for All Serogroups
Lower limit of 95% CI for the difference in seroresponders (Group 3 – Group 4) > -10%	MenA	97%	-1%	540	270	>99.99%	
	MenC	95.8%	-1%	540	270	>99.99%	
	MenW	97%	-2%	540	270	99.98%	
	MenY	94.6	-2%	540	270	99.49%	
						Power (to meet NI for all ACWY test strains)	>99.45%

Abbreviations: ACWY = meningococcal groups A, C, W, and Y; G3 and G4 = Groups 3 and 4; MenA, MenC, MenW, and MenY = *Neisseria meningitidis* groups A, C, W, and Y; NI = noninferiority.
a. Reference Study B1971057, ACWY-experienced participants.
b. At 0.05 alpha level (2-sided).

Table 9. Power Analysis for Second Primary Immunogenicity Objective

Criteria	Endpoint	MenB Strain	Reference Rate (Groups 2 + 4)[a]	Assumed Difference (G1 and G3 Combined – G2 and G4 Combined)	Number of Evaluable Participants (Groups 1 + 3 Combined)	Number of Evaluable Participants (Groups 2 + 4 Combined)	Power[b]	Power to Meet NI for All Endpoints
Lower limit of 95% CI for the difference in 4-fold rises and composite responses (Groups 1 + 3 combined – Groups 2 + 4 combined) > -10%	hSBA titer fold rise ≥4 from baseline	A22	73.8%	0	900	450	98.03%	
		A56	95%	0	900	450	>99.99%	
		B24	64.5%	0	900	450	95.64%	
		B44	86.4%	0	900	450	99.94%	
	Composite response		72.9%	0	900	450	97.80%	
							Power (to meet NI for all MenB endpoints)	>91.63%

Abbreviations: G1, G2, G3, and G4 = Groups 1, 2, 3, and 4; hSBA = serum bactericidal assay using human complement; Men B = *Neisseria meningitidis* group B; NI = noninferiority.

a. Reference Studies B1971057 and B1971012 (0-, 6-month schedule) for B24 and the composite response.
b. At 0.05 alpha level (2-sided).

There is over 90% power to demonstrate noninferiority for the secondary objective for ACWY-naïve and -experienced participants separately, evaluating the seroresponse for ACWY endpoints at 1 month following vaccination for each group.

9.2.2. Additional Participants for Safety Analysis (Groups 5-8)

The sample sizes in Groups 5, 6, 7, and 8 are not based on any hypothesis testing but rather are based on having a sufficient number of participants enrolled to sufficiently characterize the safety profile of MenABCWY. Overall, 1750 participants will be randomized to receive MenABCWY and 663 will be randomized to receive Trumenba + MenACWY-CRM. Table 10 shows the probability to detect at least 1 AE for different true incidence rates given that 1750 participants will receive MenABCWY.

Table 10. Probabilities of Detecting AEs at Specified Incidences

Sample Size	True Incidence of AE	Probability of Detecting at Least 1 AE
1750	0.001%	1.7%
1750	0.01%	16.1%
1750	0.1%	82.6%

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to investigational product	All participants who are assigned a randomization number in the IRT system.
Evaluable	Defined according to post–Vaccination 1 evaluable and post–Vaccination 2 evaluable criteria.
Modified intent-to-treat	All participants who received at least 1 study vaccination and have at least 1 valid and determinate MenB or MenA/C/W/Y assay result available at any time point from Visit 1 to Visit 4.
Safety	All randomized participants who receive at least 1 dose of the investigational product and have safety data reported after vaccination. Participants will be analyzed according to the vaccine they actually received.

Defined Population for Analysis	Description
Post–Vaccination 1 evaluable	All randomized participants who were eligible throughout Visit 2, received the investigational products at Visit 1 as randomized, had blood drawn for assay testing within the required time frames at Months 0 (Visit 1: before Vaccination 1) and 2 (Visit 2: 1 month after the first vaccination: window 28-42 days), had at least 1 valid and determinate MenA/C/W/Y assay result at Visit 2, had received no prohibited vaccines or treatment through Visit 2, and had no important protocol deviations through Visit 2. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine.
Post–Vaccination 2 evaluable	All randomized participants who were eligible throughout Visit 4, received the investigational products at Visit 1 and Visit 3 as randomized, had blood drawn for assay testing within the required time frames at Months 0 (Visit 1: before Vaccination 1) and 7 (Visit 4: 1 month after the second vaccination: window 28-42 days), had at least 1 valid and determinate MenA/C/W/Y or MenB assay result at Visit 4, had received no prohibited vaccines or treatment through Visit 4, and had no important protocol deviations through Visit 4. An important protocol deviation is a protocol deviation that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

Primary	For each of the 4 ACWY test strains, the difference in the percentages of seroresponders, defined as participants achieving a 4-fold rise from baseline, in Group 1 at 1 month after Vaccination 2 compared to Group 2 at 1 month after Vaccination 1, and also the difference in seroresponders in Group 3 at 1 month after Vaccination 2 compared to Group 4 at 1 month after Vaccination 1, will be calculated. For each of the 4 primary MenB test strains, the differences of the 4-fold rises and composite responses of Groups 1 and 3 combined compared to Groups 2 and 4 combined at 1 month after Vaccination 2 will be calculated. The Miettinen and Nurminen method will be used to derive the CI for the difference in percentages between vaccine groups. The lower limit of the CI will be used in the hypothesis test for noninferiority as detailed in Section 9.1. The analysis for the ACWY test strains is based on the post–Vaccination 1 evaluable population for Groups 2 and 4 and on the post–Vaccination 2 evaluable population for Groups 1 and 3 and the analysis for the primary MenB strains is based on the post–Vaccination 2 evaluable population in order to provide a comparison that has the greatest chance of identifying a difference between the groups with respect to immunogenicity, if a meaningful difference in vaccine effect actually exists. Exact 2-sided 95% CIs for the percentages (seroresponders, 4-fold-rises and composite responses) will be provided using the Clopper-Pearson method. A supportive analysis will be performed based on the modified intent-to-treat (mITT) population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary	For each of the 4 ACWY test strains, the difference in the percentage of seroresponders, defined as participants achieving a 4-fold rise from baseline, in Group 1 at 1 month after Vaccination 1 compared to Group 2 at 1 month after Vaccination 1, and also the differences in seroresponders between Group 3 at 1 month after Vaccination 1 and Group 4 at 1 month after Vaccination 1, will be calculated. The Miettinen and Nurminen method will be used to derive the CIs for the difference in percentages between vaccine groups. The lower limit of the CI will be used in the hypothesis test for noninferiority as detailed in Section 9.1 (conditional on the success of analysis of the primary objectives). The analysis for the ACWY test strains is based on the post–Vaccination 1 evaluable population for Groups 1, 2, 3, and 4. Percentages will be presented with 2-sided 95% CIs using the Clopper-Pearson method. Reverse cumulative distribution functions will be provided for both MenA/C/W/Y strains (1 month following Vaccination 1 for Groups 2 and 4 and 1 month following Vaccination 1 and Vaccination 2 for Groups 1 and 3) and MenB strains (1 month following Vaccination 2). Supportive analyses will be done using the mITT population. Exact 2-sided 95% CIs for the percentages will be provided using the Clopper-Pearson method. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

Tertiary/Exploratory	The following analyses for the ACWY test strains are based on the post–Vaccination 1 evaluable population for Groups 2 and 4, and on the post–Vaccination 2 evaluable population for Groups 1 and 3: The percentage of participants achieving an hSBA titer ≥1:8 for each ACWY test strain, at baseline and 1 month after Vaccination 1 in Groups 2 and 4, and 1 month after Vaccination 2 in Groups 1 and 3. The percentage of participants achieving hSBA titers of ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each ACWY test strain, at baseline, 1 month after Vaccination 1 in Groups 2 and 4, and 1 month after Vaccination 2 in Groups 1 and 3. hSBA GMTs for each of the ACWY test strains, at baseline, 1 month after Vaccination 1 in Groups 2 and 4, and 1 month after Vaccination 2 in Groups 1 and 3. The following analyses for the ACWY test strains are based on the post–Vaccination 1 evaluable population for all groups: • The percentage of participants achieving an hSBA titer ≥1:8 for each ACWY test strain, at baseline and 1 month after Vaccination 1 in Groups 1 through 4. • The percentage of participants achieving hSBA titers of ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each ACWY test strain, at baseline and 1 month after Vaccination 1 in Groups 1 through 4. • hSBA GMTs for each of the ACWY test strains, at baseline and 1 month after Vaccination 1 in Groups 1 through 4. The following analyses are for the primary MenB test strains: The percentage of participants achieving an hSBA titer ≥ LLOQ (1:16 for A22 and 1:8 for A56, B24, and B44) for each primary MenB test strain in Groups 1 + 3 combined and Groups 2 + 4 combined, at baseline and 1 month after Vaccination 2, will be summarized using the post–Vaccination 2 evaluable population. The percentage of participants with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB test strains in Groups 1 + 3 combined and Groups 2 + 4 combined, at baseline and 1 month after Vaccination 2, will be summarized using the post–Vaccination 2 evaluable population. MenB hSBA GMTs for each of the 4 primary MenB test strains in Groups 1 + 3 combined and Groups 2 + 4 combined, at baseline and 1 month after Vaccination 2, will be summarized using the post–Vaccination 2 evaluable population. The percentage of participants achieving an hSBA titer ≥ LLOQ for each secondary MenB test strain in Groups 1 + 3 combined, at baseline and 1 month after Vaccination 2, will be summarized using the post–Vaccination 2 evaluable population. The percentage of participants with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the secondary MenB test strains in Groups 1 + 3 combined, at baseline and 1 month after Vaccination 2, will be summarized using the post–Vaccination 2 evaluable population. hSBA GMTs for each of the secondary MenB test strains in Groups 1 + 3 combined, at baseline and 1 month after Vaccination 2, will be summarized using the post–Vaccination 2 evaluable population. Percentages will be presented with 2-sided 95% CIs using the Clopper-Pearson method. Geometric means and their 2-sided CIs will be derived by calculating means and CIs on the natural log scale based on the t-distribution, and then exponentiating the results. Titers below LLOQ will be set to 0.5 × LLOQ for analysis.

	Supportive analyses will be done using the mITT population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population. Separate safety populations will be defined for each vaccination visit and follow-up phase, Vaccination 1, Vaccination 2, and follow-up phase, and will be detailed in the SAP.

Endpoint	**Statistical Analysis Methods**
Primary	The proportion of participants reporting local reactions at the investigational product administration site and systemic events within the 7-day period after each vaccination will be descriptively summarized by MenABCWY and Trumenba combined groups (ie, Groups 1, 3, 5, and 7 combined compared to Groups 2, 4, 6, and 8 combined). Two (2)-sided 95% CIs based on the Clopper-Pearson method will be presented with the proportions. Severities of local reactions and systemic events reported after each vaccination will also be descriptively summarized by the same MenABCWY and Trumenba combined groups. Local reactions will be summarized only for the left arm, which is the MenABCWY or Trumenba injection site. The proportion of participants reporting the use of antipyretic medication for Days 1 to 7 will be compiled for MenABCWY and Trumenba combined groups after each vaccination. All AEs and SAEs will be categorized according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). An MAE is defined as a nonserious AE that results in an evaluation at a medical facility. An NDCMC is defined as a disease or medical condition not previously identified that is expected to be persistent or otherwise long-lasting in its effects. AEs, SAEs, MAEs, and NDCMCs will be summarized by vaccine group. A 3-tier approach will be used to summarize AEs. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance; (2) Tier 2 events are those that are not Tier 1 but are considered "relatively common"; a MedDRA preferred term is defined as a Tier 2 event if there are at least 4 participants in at least 1 (combined) vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, the 95% CIs for the difference in percentage of participants reporting the events between MenABCWY and Trumenba combined groups will be calculated using the Miettinen and Nurminen method. There is no Tier 1 event identified for MenABCWY at this stage. Descriptive summary statistics (counts and percentages and associated Clopper-Pearson 95% CIs) will be provided for Tier 3 events for MenABCWY and Trumenba combined groups. Participants will be analyzed according to the vaccine they actually received. Missing e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules. Detailed analyses for each safety endpoint will be addressed in the SAP.
Secondary	Not applicable.
Tertiary/Exploratory	Not applicable.

9.5. Interim Analyses

No interim analysis is planned for the study. Only 1 analysis will be performed at the completion of the study.

9.5.1. Data Monitoring Committee

This study will use an E-DMC.

An independent statistician will provide unblinded safety reports to the E-DMC for review. Safety data will be reviewed by the E-DMC throughout the study, and no adjustments to the type I error for the noninferiority assessments will be made for these periodic safety reviews.

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, IB, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her parent(s)/legal guardian and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant or his or her parent(s)/legal guardian must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant or his or her parent(s)/legal guardian must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the parent(s)/legal guardian.

A study-specific assent form will be provided to pediatric participants as required by local regulations. It is to be understood as the adolescent's will to participate in a trial after having received age-appropriate information and is sometimes also referred to as "knowing agreement." If the study includes minor participants who reach the age of majority during the study, as recognized under local law, they must reconsent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code.

Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT)/Clinical Trial Information System (CTIS), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs and SAPs. Clinical documents will have personally identifiable information anonymized.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the SRM.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the investigator site file.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study.

The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

Not applicable.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of an NDCMC

An NDCMC is defined as a disease or medical condition, not previously identified, that is expected to be persistent or is otherwise long-lasting in its effects.

10.3.3. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. **Results in death**
b. **Is life-threatening** The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. **Requires inpatient hospitalization or prolongation of existing hospitalization** In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. **Results in persistent disability/incapacity** • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

An SAE is defined as any untoward medical occurrence that, at any dose:
e. **Is a congenital anomaly/birth defect**
f. **Other situations:** • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Reporting Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Reporting Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Reporting Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Reporting Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

Follow-up of AEs and SAEs
• If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.5. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form
• Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention:

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception is recommended in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

   - Documented hysterectomy;

   - Documented bilateral salpingectomy;

   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).

     - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner:

   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

   - oral;
   - intravaginal;
   - transdermal;
   - injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - oral;
   - injectable.

8. Sexual abstinence:

   - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

Collection of Pregnancy Information

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI.

Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.6. Appendix 6: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.2) for the list of sponsor medical devices).

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health. • Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of healthcare personnel.

It is sufficient that:

- An **incident** associated with a device happened.

AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness;
- Permanent impairment of body function or permanent damage to body structure;
- Condition necessitating medical or surgical intervention to prevent one of the above;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

Examples of Incidents
• A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. • A participant's study intervention is interrupted or compromised by a medical device failure. • A misdiagnosis due to medical device failure leads to inappropriate treatment. • A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documentation
• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the CRF. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 3. • The CRF will be completed as thoroughly as possible and signed by the investigator before transmittal to the sponsor or designee. • It is very important that the unblinded site staff provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

10.7. Appendix 7: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ACIP	Advisory Committee on Immunization Practices
ACWY	meningococcal group A, C, W, and Y
AE	adverse event
$AlPO_4$	aluminum phosphate
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bivalent rLP2086	bivalent recombinant lipoprotein 2086 vaccine (Trumenba)
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDP	clinical development program
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	coronavirus disease 2019
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CRF	case report form
CRM	cross-reactive material
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
DTaP-Hib	diphtheria, tetanus, and acellular pertussis and *Haemophilus influenzae* type b vaccine
dTaP-IPV	diphtheria, tetanus, and acellular pertussis and inactivated poliomyelitis virus vaccine
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
fHBP	factor H binding protein
FIH	first-in-human
FSH	follicle-stimulating hormone

Abbreviation	Term
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMT	geometric mean titer
GSK	GlaxoSmithKline
HBV-IPV	hepatitis B virus and inactivated poliomyelitis virus vaccine
HIPAA	Health Insurance Portability and Accountability Act
HPV4	human papillomavirus vaccine
HRT	hormone replacement therapy
hSBA	serum bactericidal assay using human complement
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IMD	invasive meningococcal disease
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
IP manual	investigational product manual
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IVRS	interactive voice response system
IWRS	interactive Web-based response system
LFT	liver function test
LLOQ	lower limit of quantitation
LOD	limit of detection
MAE	medically attended adverse event
MCAR	missing completely at random
MCV4-Tdap	quadrivalent meningococcal polysaccharide conjugate and diphtheria, tetanus, and acellular pertussis vaccine
MedDRA	Medical Dictionary for Regulatory Activities
MenA	*Neisseria meningitidis* group A
MenABCWY	*Neisseria meningitidis* group A, B, C, W, and Y vaccine
MenACWY-CRM	meningococcal groups A, C, Y, and W-135 oligosaccharide diphtheria conjugate vaccine (Menveo)
MenACWY-TT	meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine (Nimenrix)
MenB	*Neisseria meningitidis* group B
MenC	*Neisseria meningitidis* group C
MenCYW-135	meningococcal group C, Y, and W-135
MenW	*Neisseria meningitidis* group W

Abbreviation	Term
MenY	*Neisseria meningitidis* group Y
mITT	modified intent-to-treat
NDCMC	newly diagnosed chronic medical condition
NIMP	noninvestigational medicinal product
PACL	protocol administrative change letter
PCD	primary completion date
PFS	prefilled syringe
POC	proof of concept
PRP-OMP	polyribosylribitol phosphate oligosaccharide of *Haemophilus influenzae* type b conjugated to outer membrane protein
PT	prothrombin time
rSBA	serum bactericidal assay using rabbit complement
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOP	standard operating procedure
SRM	study reference manual
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
ULN	upper limit of normal
US	United States
USPI	US package insert
WOCBP	woman/women of childbearing potential

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Signed By:	Date(GMT)	Signing Capacity
PPD		
PPD		